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Symposium on Verapamil Therapy for Angina Pectoris: Parts I and II

Milton Packer, Guest Editor, and William H. Frishman, Guest Co-Editor

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ADDRESS MANUSCRIPTS TO:
William C. Roberts, MD, Editor-in-Chief
THE AMERICAN JOURNAL OF CARDIOLOGY
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When more than a thiazide is needed...

ALDOMET® TABLETS 500 mg, 250 mg, and 125 mg

(METHYLDOPA | MSD

an agent well matched to the profile

With increasing age...
incidence of certain concurrent disorders increases

ALDOMET may be used in a wide range of older hypertensives, including those with:

- **ventricular hypertrophy/cardiac failure***
- **peripheral vascular disease**
- **diabetes mellitus**
- **hyperuricemia/gouty arthritis**

judicious exercise may be desirable

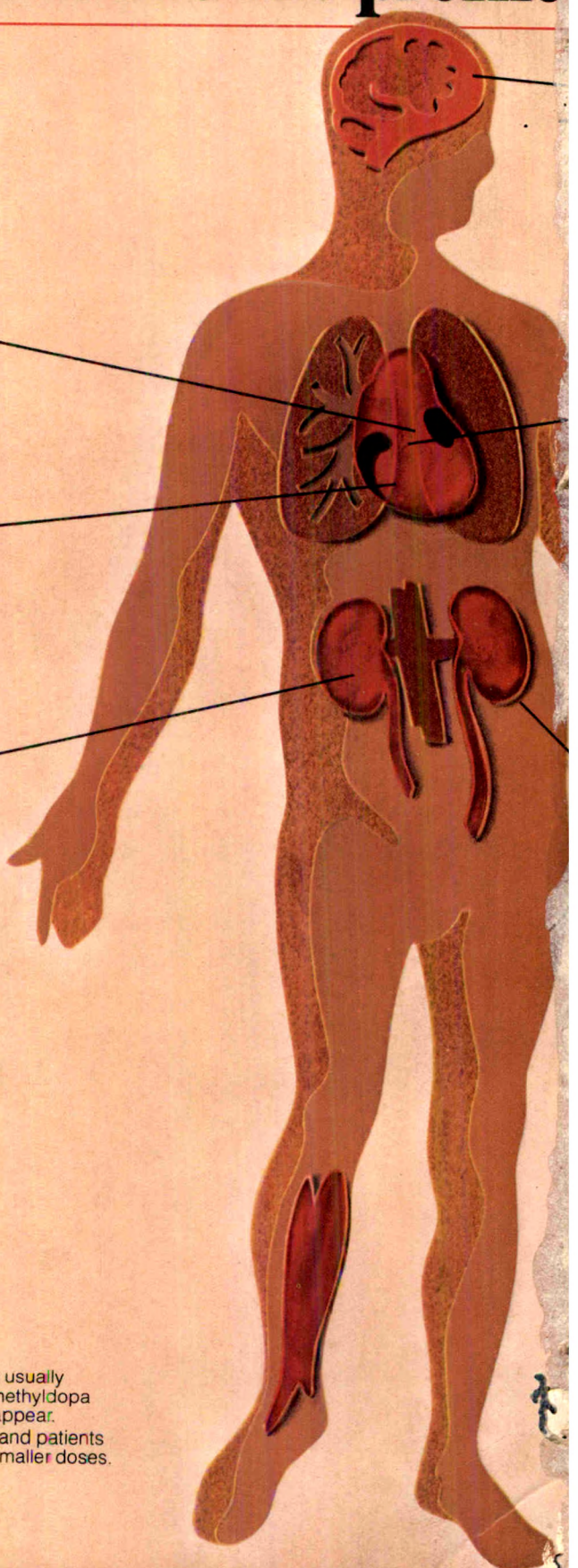
ALDOMET usually does not interfere with the cardiovascular response to exercise.

renal function often diminished

ALDOMET usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction.†

compliance often a problem

ALDOMET provides b.i.d. dosage convenience for many patients.



*Edema (and weight gain) may occur and may usually be relieved by use of a diuretic. Discontinue methyldopa if edema progresses or signs of heart failure appear.

†Methyldopa is largely excreted by the kidney, and patients with impaired renal function may respond to smaller doses.

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# of a wide range of older hypertensives

ability to autoregulate cerebral blood flow with postural changes often decreased

With ALDOMET® (Methyldopa, MSD), symptomatic postural hypotension is infrequent. Syncope in older patients may be avoided by lower doses.

cardiac output and heart rate usually normal

ALDOMET has no direct effect on cardiac function, and cardiac output usually is maintained.

total peripheral resistance usually high

ALDOMET lowers blood pressure, apparently by lowering total peripheral resistance.

ongoing therapy usually required

ALDOMET has demonstrated a high degree of efficacy in long-term therapy.

plasma renin activity usually low but may be normal or high

With ALDOMET, normal or elevated plasma renin activity may decrease.

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, or if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed.

Syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease. This may be avoided by lower doses.

MSD
MERCK SHARP & DOHME

For a Brief Summary of Prescribing Information, please see following page.

ALDOMET® (Methyldopa/MSD)

Tablets, containing 125, 250, or 500 mg methyldopa; Oral Suspension, containing 250 mg methyldopa per 5 ml and alcohol 1%.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions. With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood. At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients. Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, prolonged carotid sinus hypersensitivity, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, colitis, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Bone marrow depression, leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Dermatologic:* Rash as in eczema or lichenoid eruption; toxic epidermal necrolysis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, hyperprolactinemia, amenorrhea, impotence, decreased libido, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, PA 19486

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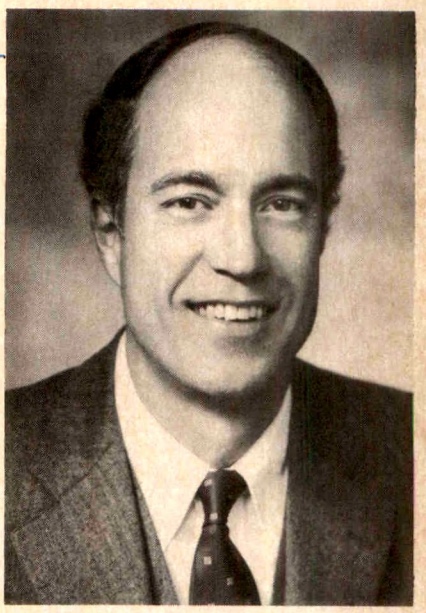


The Editorial Board

Shortly after becoming Editor of the *AJC*, I began reflecting on physicians who I would ask to serve as editorial board members. I realized immediately that a *large board* would be essential if the board members, rather than outside consultants, were to be the primary reviewers of manuscripts submitted to the *Journal*. Each major and minor subspecialty of cardiology needed to be represented by several respected investigators. I was particularly anxious to increase the representation of cardiovascular surgeons because their role is a vital one in the present-day management of patients with cardiovascular disease, and because in the past they have been underrepresented on the boards of cardiology journals.

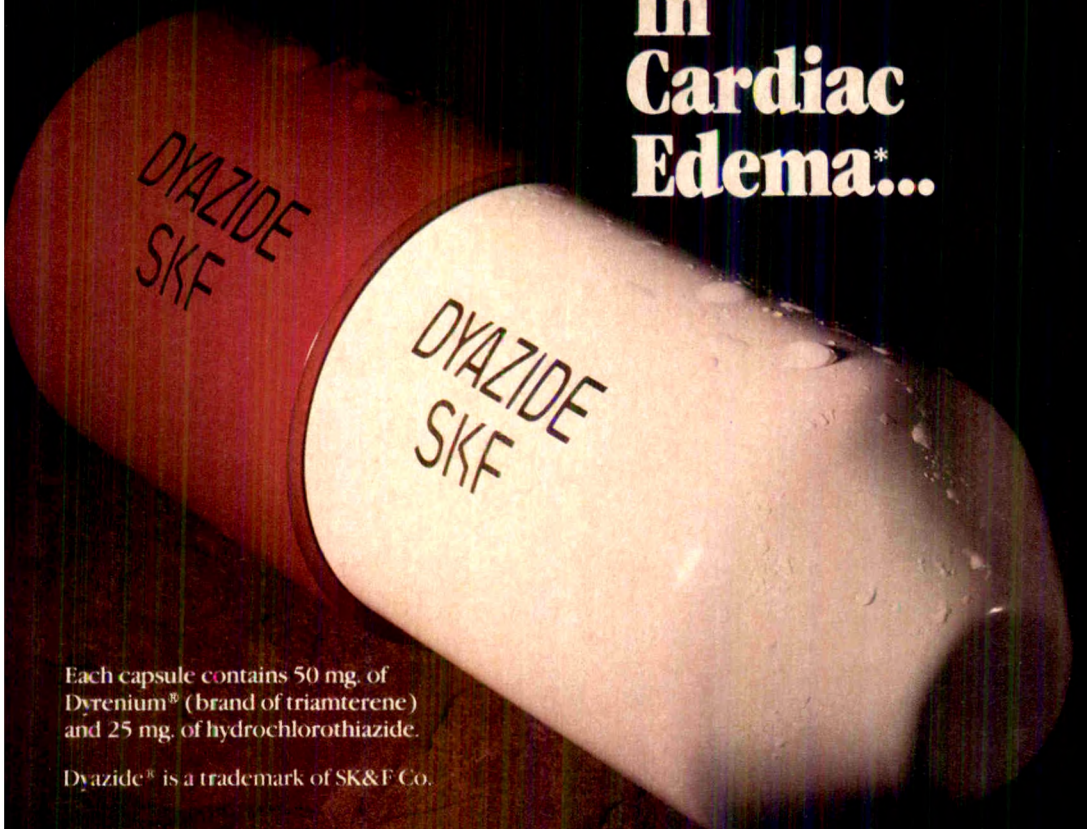
I also realized immediately that many individuals I would want on the new editorial board would already be members of one or more other editorial boards. In the past I have had the privilege of serving simultaneously on the editorial boards of 6 different medical journals, and as a reviewer I have paid little attention to the name of the journal for which I was reviewing a manuscript. An editorial board member's expertise is not the monopoly of a single medical journal. The board member's charge is to evaluate promptly the scientific quality of a manuscript and the means to improve that manuscript. Board-member reviewers, as do nonboard reviewers, serve the entire medical community by providing expert opinions to any editor who asks them to do so. They do not and should not take a loyalty oath to a specific journal—their loyalty is to the writer and the reader. Placing a reviewer on an editorial board gives him public recognition as a superb manuscript reviewer and is the means by which the editor says "thanks" for his help. If one editor rewards a reviewer by placing him on his editorial board, that action should not prevent another editor from rewarding the same reviewer similarly. Indeed, membership on more than one editorial board is further acknowledgment of a reviewer's sought-after expertise. Just as the medical writer (investigator) is free to submit his manuscript to any journal he chooses, the expert reviewer is free to provide his expertise to any journal so requesting. If an *AJC* board member is a member of another editorial board, that is the business of the editorial board member and the other journal, and of no concern to the present Editor of the *AJC*.

After establishing the principle that a large editorial board would be necessary, I prepared lists of adult and pediatric cardiologists, cardiac surgeons, and related specialists such as radiologists, pathologists, and pharmacologists, and in July 1982 I began dialing the telephone. I initially contacted 110 potential editorial board members, 103 of whom accepted the invitation. I am grateful and indeed the entire cardiovascular community must be grateful to these expert manuscript reviewers who devote their time freely to improving the quality of articles published in our medical journals.

William C. Roberts

William C. Roberts, MD
Editor-in-Chief

In Cardiac Edema*...



Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Dyazide® is a trademark of SK&F Co.

When You Need to Conserve K^+

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, Dyazide should be used with caution in patients with histories of stone formation. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. Dyazide interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and Dyazide should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of Dyazide, although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak® unit-of-use bottles of 100.

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ARRHYTHMIAS

Cardiovascular well-being often begins with Inderal®
(PROPRANOLOL HCl)

No agent offers a better risk/benefit profile in arrhythmias than INDERAL (propranolol HCl). INDERAL works to reduce heart rate and contractility, lengthen A-V conduction time, and suppress automaticity[1]—helping to restore the heart rate to normal in many patients with a wide variety of arrhythmias.

Consider INDERAL for arrhythmias early—to restore cardiovascular well-being as soon as possible.

Reference: 1. AMA Department of Drugs: AMA Drug Evaluations, ed. 4. Littleton, Mass., Publishing Sciences Group, Inc., 1980, p. 520.

Please see Brief Summary of Prescribing Information on the following page.

INDERAL®
(PROPRANOLOL HCl)
The sooner, the better.

INDERAL®
(PROPRANOLOL HCl)

To restore cardiovascular well-being.

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
Inderal® (propranolol hydrochloride)

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

CONTRAINDICATIONS

1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless it is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: In congestive heart failure, inhibition with beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In patients already receiving digitalis, propranolol may reduce the positive inotropic action of digitalis and may have an additive depressant effect on AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, in rare instances, cardiac failure has developed during propranolol therapy. At the first sign of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Give special consideration to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol should be withdrawn slowly, since abrupt withdrawal may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta-blockade impairs the ability of the heart to respond to reflex stimuli. Except in pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery. In case of emergency surgery, the effects of propranolol can be reversed by administration of beta-receptor agonists such as isoproterenol or levarterenol, but such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), administer with caution, since propranolol may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in patients with labile diabetes. A precipitous elevation of blood pressure may accompany hypoglycemic attacks.

USE IN PREGNANCY: Safe use in human pregnancy not established. Embryotoxic effects have been seen in animals at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if propranolol is administered, since it may occasionally produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

Observe laboratory parameters at regular intervals. Use with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure, intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta-blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

HOW SUPPLIED

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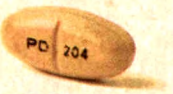

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A Brief Summary follows.

The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

INDICATIONS AND USAGE: Oral procainamide is indicated in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS: It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross-sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block. Procainamide is also contraindicated in cases of second-degree and third-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: General —During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient reevaluated since asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney disease, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Instances of a syndrome resembling lupus erythematosus have been reported in connection with maintenance procainamide therapy. The mechanism of this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain are common symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural effusion, and pericarditis may occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia have been reported which may be related to this syndrome.

Laboratory Tests —Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals. The drug should be discontinued if there is a rising titer (antinuclear antibody) or clinical symptoms of LE appear. The LE syndrome may be reversible upon discontinuation of the drug. If discontinuation of the drug does not cause remission of the symptoms, steroid therapy may be effective. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, steroid suppressive therapy may be used concomitantly with procainamide. It is recommended that tests for lupus erythematosus be carried out at regular intervals in patients receiving maintenance procainamide therapy.

Routine blood counts are advisable during maintenance procainamide therapy.

ADVERSE REACTIONS: Agranulocytosis has occasionally followed the repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tract infection. If any of these should occur, and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

A syndrome resembling lupus erythematosus has been reported (see PRECAUTIONS).

Hypotension following oral administration is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills have also been reported, including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Bitter taste, diarrhea, weakness, mental depression, giddiness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

DOSAGE AND ADMINISTRATION: Procan SR (procainamide hydrochloride) tablets are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every six hours instead of the more frequent every-three-hour dosing interval required for standard preparations of oral procainamide hydrochloride. The convenient six-hour dosing schedule may encourage patient compliance.

Ventricular tachycardia —Treatment with standard procainamide hydrochloride is recommended until the tachycardia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows: An initial dose of 1 g of standard procainamide hydrochloride followed thereafter by a total daily dose of 50 mg/kg of body weight given at three hour intervals. The suggested oral dosage for premature ventricular contractions is 50 mg/kg of body weight daily given in divided doses at three-hour intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg of body weight daily given in divided doses at six-hour intervals.

Although the dosage for each patient must be determined on an individual basis, the following may be used as a guide for providing the total daily dosage: patients weighing less than 55 kg (120 lb), 0.5 g every six hours; patients weighing between 55 and 91 kg (120 and 200 lb), 0.75 g every six hours; and patients weighing over 91 kg (200 lb), 1 g every six hours.

Atrial fibrillation and paroxysmal atrial tachycardia —Treatment with standard procainamide hydrochloride is recommended until the arrhythmia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Standard procainamide hydrochloride may then be given at a dose of 0.5 to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every six hours.

If procainamide therapy is continued for appreciable periods, electrocardiograms should be made occasionally to determine the need for the drug.

HOW SUPPLIED: Procan SR 250 mg (green, film-coated tablet, P-D 202) is available in bottles of 100 (N 0071-0202-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0202-40). Each sustained-release tablet contains 250 mg procainamide hydrochloride.

Procan SR 500 mg (yellow, scored, film-coated tablet, P-D 204) is available in bottles of 100 (N 0071-0204-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0204-40). Each sustained-release tablet contains 500 mg procainamide hydrochloride.

Procan SR 750 mg (orange, scored, film-coated tablet, P-D 205) is available in bottles of 100 (N 0071-0205-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0205-40). Each sustained-release tablet contains 750 mg procainamide hydrochloride.

Storage—Protect from moisture. Store bottles below 86° F (30° C). Store unit-dose packages at controlled room temperature, 59°-86° F (15°-30° C).

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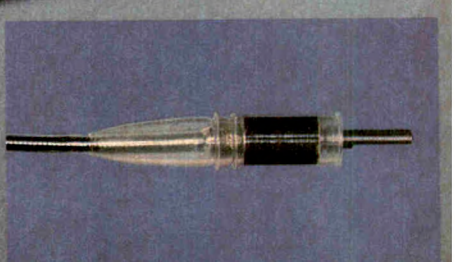

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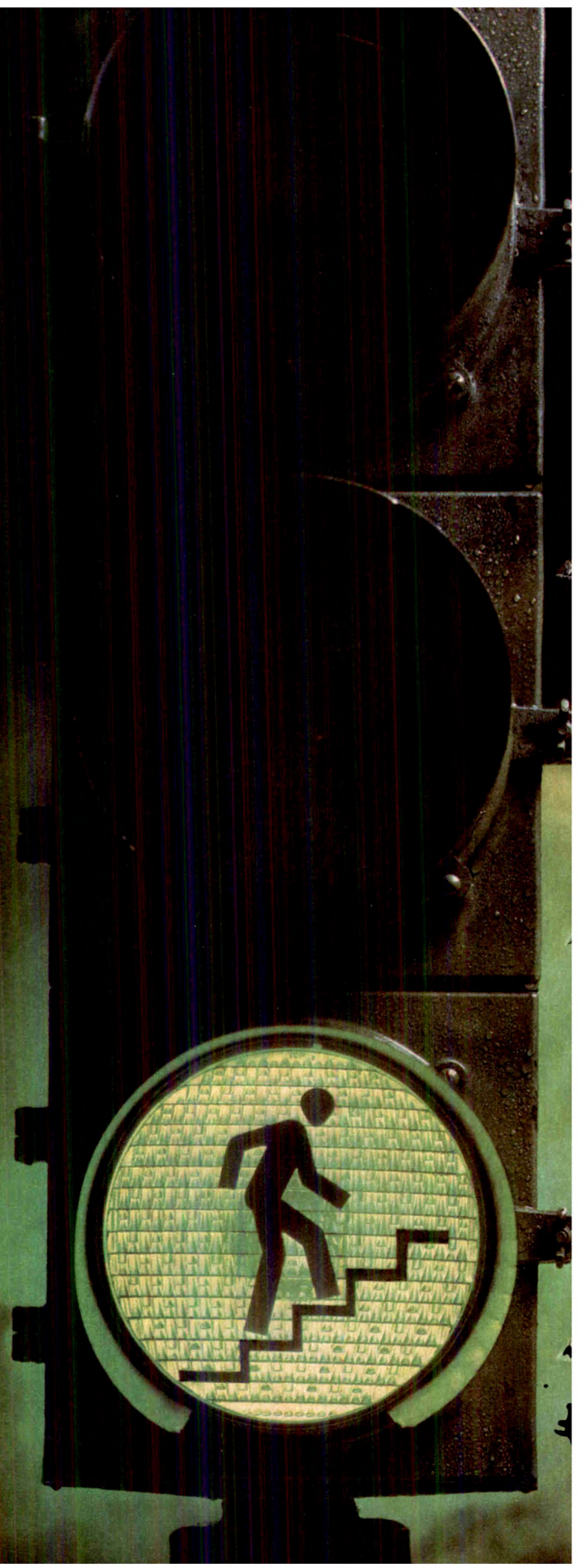

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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before Calan is used. Calan may occasionally produce hypotension usually asymptomatic, orthostatic, mild, and controlled by decrease in Calan dose. Occasional elevations of liver enzymes have been reported; patients receiving verapamil should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) may develop a very rapid ventricular response after receiving verapamil (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil. **Precautions:** Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of Calan and beta-blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, verapamil should be used alone if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with verapamil and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic verapamil treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil may have an additive hypotensive effect in patients receiving blood-pressure lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd-degree (0.8%), bradycardia: HR < 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, maculae, and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients. **How Supplied:** Calan (verapamil HCl) is supplied in 80-mg and 120-mg sugar-coated tablets.

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2W5

From the American Journal of Medicine

NOSOCOMIAL INFECTIONS

edited by
Richard E. Dixon, M.D.

appx. 344p June 1981,
$29.50 hardbound
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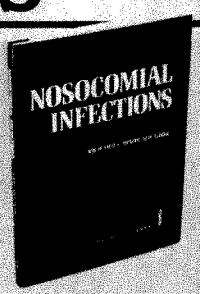

Based on the proceedings of the 2nd International Conference on Nosocomial Infections held August 5 - 8, 1980 in Atlanta, Georgia and sponsored by the Center for Disease Control, this book provides between two covers the most comprehensive, in-depth study of this international problem published in 10 years. This major reference is divided into 11 sections consisting of 50 chapters written by over 100 internationally known experts.

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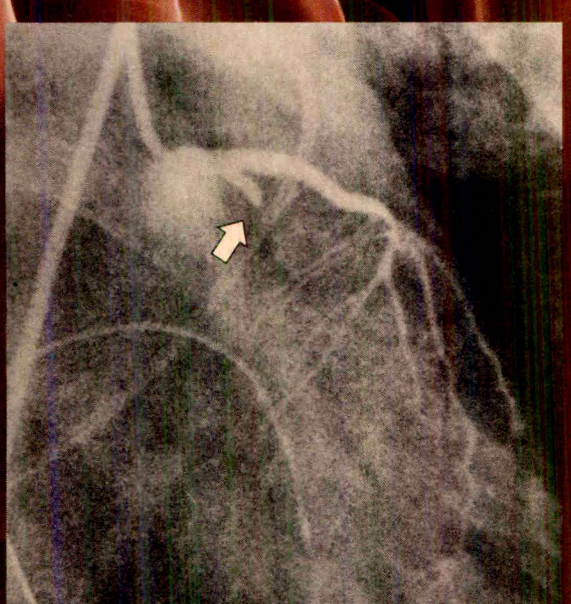
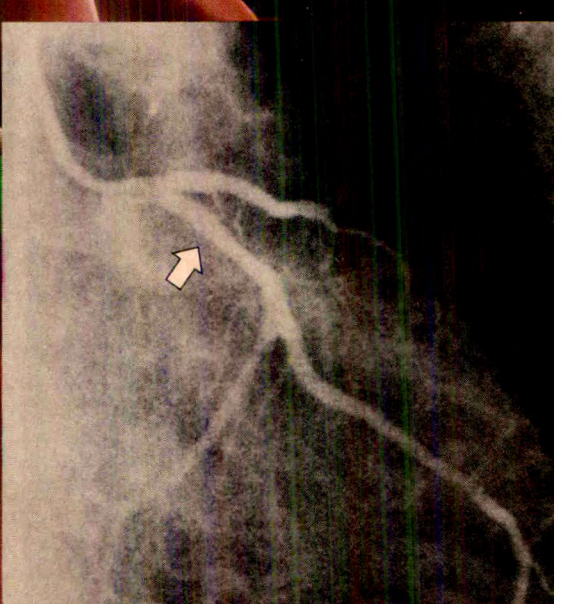
New therapy quickly dissolves acute coronary artery thrombi



Pre-streptokinase
A 38-year-old woman in cardiogenic shock with acute lateral wall myocardial infarction caused by complete left circumflex occlusion (arrow).



Post-streptokinase
The left circumflex is now widely patent beyond previous site of obstruction (arrow).

Please see full prescribing information, a summary of which appears on the last page of this ad.

STREPTASE®
(streptokinase)

now indicated for acute coronary artery thrombosis.

Streptase® is infused directly into the involved artery during cardiac catheterization.

Efficacy demonstrated in multicenter studies

Coronary artery reperfusion was accomplished in 174 of 221 patients (79%) during evolving transmural myocardial infarction.

Randomized, controlled studies are in progress to determine the effects of reperfusion on salvage of myocardial tissue and reduction of mortality.

Side effects: few and readily controlled

There were no reports of allergic reaction or fever. Seven cases of bleeding at the puncture site and one case of moderate peritoneal bleeding were controlled without terminating therapy. Severe bleeding was reported in only one patient. This patient had a gastric ulcer six months prior to treatment.

Prompt initiation of treatment critical

The greatest benefit is achieved when therapy is initiated within six hours after the onset of symptoms.

Thrombolytic activity and safety record well documented

Streptase® has been effectively used worldwide for nearly a decade. Its record of clinical success is well matched by its record of safety, and both have been extensively reported in the medical literature.

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A major advance in M.I. therapy

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STREPTASE® (streptokinase)
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INDICATIONS AND USAGE

CORONARY ARTERY THROMBOSIS

Streptase® (streptokinase) has been reported to lyse acute thrombi obstructing coronary arteries, associated with evolving transmural myocardial infarction. Diagnosis of acute myocardial infarction has been confirmed, and the site of coronary thrombosis identified by selective coronary angiography. Other studies have demonstrated that (a) a thrombus is present in approximately 90% of patients evaluated within four hours of onset of symptoms; (b) when compared to concurrent or historical controls, the majority of patients who received intracoronary streptokinase within 6 hours of onset of symptoms showed a more immediate recanalization (within a few minutes vs hours/days) of the involved vessel.

IT HAS NOT BEEN ESTABLISHED THAT INTRACORONARY ADMINISTRATION OF STREPTOKINASE DURING EVOLVING TRANSMURAL MYOCARDIAL INFARCTION RESULTS IN SALVAGE OF MYOCARDIAL TISSUE, NOR THAT IT REDUCES MORTALITY. CONTROLLED STUDIES ADDRESSING THESE PARAMETERS ARE IN PROGRESS AND UNTIL COMPLETED, THOSE PATIENTS WHO MIGHT BENEFIT FROM THIS THERAPY CANNOT BE DEFINED.

CONTRAINDICATIONS

Because thrombolytic therapy increases the risk of bleeding, Streptase® (streptokinase) is contraindicated in the following situations:

- active internal bleeding
- recent (within 2 months) cerebrovascular accident, intracranial or intraspinal surgery (see WARNINGS)
- intracranial neoplasm

WARNINGS

Bleeding

The aim of Streptase® (streptokinase) therapy is the production of sufficient amounts of plasmin for the lysis of intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example, at sites of needle punctures, are also lysed and bleeding from such sites may occur.

Intramuscular injections and nonessential handling of the patient must be avoided during treatment with Streptase® (streptokinase). Venipunctures should be performed carefully and as infrequently as possible.

Should an arterial puncture be necessary during intravenous therapy, upper extremity vessels are preferable. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

When internal bleeding occurs, it may be more difficult to manage than that which occurs with conventional anticoagulant therapy.

In the following conditions the risks of therapy may be increased and should be weighed against the anticipated benefits.

- Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels
- Recent serious gastrointestinal bleeding (within 10 days)
- Recent trauma including cardiopulmonary resuscitation
- Severe, uncontrolled arterial hypertension
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Subacute bacterial endocarditis
- Hemostatic defects including those secondary to severe hepatic or renal disease
- Pregnancy
- Cerebrovascular disease
- Diabetic hemorrhagic retinopathy
- Prior severe allergic reaction to streptokinase
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Should serious spontaneous bleeding (not controllable by local pressure) occur, the infusion of Streptase® (streptokinase) should be terminated immediately and treatment instituted as described under ADVERSE REACTIONS.

Use of Anticoagulants

Concurrent use of anticoagulants with intravenous administration of Streptase® (streptokinase) is not recommended. However, concurrent use of heparin may be required during intracoronary administration of Streptase® (streptokinase). Clinical studies with concurrent use of heparin and lower Streptase® (streptokinase) dosages employed during intracoronary administration have demonstrated no tendency toward increased bleeding that would not be attributable to the procedure or Streptase® (streptokinase) alone. Nevertheless, careful monitoring for excessive bleeding is advised.

Arrhythmias

Rapid lysis of coronary thrombi has been reported occasionally to cause reperfusion atrial or ventricular dysrhythmias requiring immediate treatment. During studies, careful monitoring for arrhythmia was maintained during and immediately following intracoronary administration of Streptase® (streptokinase).

PRECAUTIONS

Use in Pregnancy and Children

Safety and effectiveness of Streptase® (streptokinase) therapy in children and during pregnancy have not been established. Therefore, treatment of such patients is not recommended.

Drug Interactions

The interaction of Streptase® (streptokinase) with other drugs has not been studied. Drugs that alter platelet function should not be used during therapy. Common examples are: aspirin, indomethacin, and phenylbutazone.

Patient Monitoring

Before commencing thrombolytic therapy, it is desirable to obtain a thrombin time (TT), activated partial thromboplastin time (APTT), prothrombin time (PT), hematocrit and platelet count to obtain hemostatic status of the patient.

Intracoronary Artery Infusion

During studies, laboratory monitoring of hemostatic parameters during intracoronary artery infusion showed minimal changes, if any. Heparin was continued during therapy or instituted following therapy and monitored accordingly.

ADVERSE REACTIONS

The following adverse reactions have been frequently associated with intravenous therapy but may also occur with intracoronary artery infusion:

Bleeding

Minor bleeding occurs often with thrombolytic therapy mainly at invaded or disturbed sites. When lytic therapy is continued while local measures are used to control minor bleeding, do not reduce the dose as this will increase lytic activity since more plasminogen will be available for conversion to plasmin. Severe internal bleeding involving gastrointestinal, genitourinary, retroperitoneal or intracerebral sites, may occur. Several fatalities due to cerebral and other serious internal hemorrhage have occurred during intravenous thrombolytic therapy.

Should uncontrollable bleeding occur, Streptase® (streptokinase) infusion should be discontinued and, if necessary, blood loss and reversal of the bleeding tendency can be effectively managed with whole blood (fresh blood preferable), packed red blood cells and cryoprecipitate or fresh frozen plasma. Although the use of aminocaproic acid (ACA, AMICAR®) in humans as an antidote for streptokinase has not been documented, it may be considered in an emergency situation.

Allergic Reactions

Reactions attributed to possible anaphylaxis have been observed rarely in patients treated with Streptase® (streptokinase) intravenously. These ranged in severity from minor breathing difficulty to bronchospasm, periorbital swelling or angioneurotic edema. Other milder allergic effects such as urticaria, itching, flushing, nausea, headache and musculoskeletal pain have also been observed.

Mild or moderate reactions may be managed with concomitant antihistamine and/or corticosteroid therapy. Severe allergic reactions require immediate discontinuation of Streptase® (streptokinase), with adrenergics, antihistamines, or corticosteroids administered intravenously as required.

Fever

Although Streptase® (streptokinase) is nonpyrogenic in standard animal tests, approximately one-third of patients treated with Streptase® (streptokinase) intravenously have shown increases in body temperature of ≥ 1.5°F. Symptomatic treatment is usually sufficient to alleviate discomfort. The use of acetaminophen rather than aspirin is recommended.

DOSAGE AND ADMINISTRATION

Lysis of Coronary Artery Thrombi

During clinical studies, Streptase® (streptokinase) was administered selectively into the thrombosed coronary artery via coronary catheter placed by the Judkins or Sones Technique. When administered within 6 hours of onset of symptoms of acute transmural myocardial infarction, at a bolus dose averaging 20,000 IU and a maintenance dose averaging 2,000 IU/min for 60 minutes, greater than 75% of occlusions were opened in less than 1 hour.

How Supplied

Streptase® (streptokinase) is supplied as a lyophilized white powder in 6.5 mL vials (in packages of 10) with color-coded labels corresponding to the amount of purified Streptase® (streptokinase) in each vial as follows:

green — 250,000 IU blue — 750,000 IU

Store unopened vials at controlled room temperature (15-30°C).

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CLINICAL STUDIES

663 Medical Versus Surgical Treatment of Unstable Angina

HERBERT N. HULTGREN, UDIPI R. SHETTIGAR, and D. CRAIG MILLER

A prospective, nonrandomized data bank study of the effect of medical versus surgical management of unstable angina included all patients with unstable angina seen at 1 hospital over an 8 year period. All patients had an initial 5 day period of medical treatment. Surgery was performed in 104 patients (operative mortality 2%) and medical treatment was continued in 124 patients. After a mean follow-up period of 52 months, 7 year survival (Mantel-Haenszel) was 65% for the medical group and 85% for the surgical group when analyzed by initial treatment ($p = 0.012$). Analysis of survival by the crossover method where crossover medical patients are followed only to the date of surgery showed a similar improvement in survival in surgical patients ($p = 0.008$). Nonsurvivors had a higher incidence of the following entry features than survivors: (1) age greater than 60 years, (2) diastolic hypertension, (3) ST-T changes at rest, (4) 3 vessel disease, and (5) elevated left ventricular diastolic pressure. No patient who died had single-vessel disease. Surgical treatment improves survival in patients with unstable angina, especially those with adverse prognostic features.

671 Characteristics of Survivors of Exertion- and Nonexertion-Related Cardiac Arrest: Value of Subsequent Exercise Testing

W. DOUGLAS WEAVER, LEONARD B. COBB, and ALFRED P. HALLSTROM

Ninety ambulatory patients who had previously been resuscitated from out-of-hospital ventricular fibrillation had subsequent exercise testing and further follow-up to determine possible predictors of further episodes of cardiac arrest. About one third had had the initial episode of cardiac arrest during exertion-related activities, and 30% of the total group of 90 patients died during the 2 year follow-up. There was no greater evidence of "ischemia" before cardiac arrest in those with exertion-related cardiac arrest than in the nonexertion group. Exercise testing provoked a similar incidence of S-T depression; complex ectopy was evoked more often in the nonexertion-related group. Exercise test-evoked angina or failure to augment systolic blood pressure were strongly associated with subsequent fatal events during the follow-up period. There were no clinical or exercise characteristics unique to patients who collapsed during exertion. Routine exercise testing was of limited value in predicting subsequent fatal events in patients previously resuscitated from ventricular fibrillation.

Continued on Page A26

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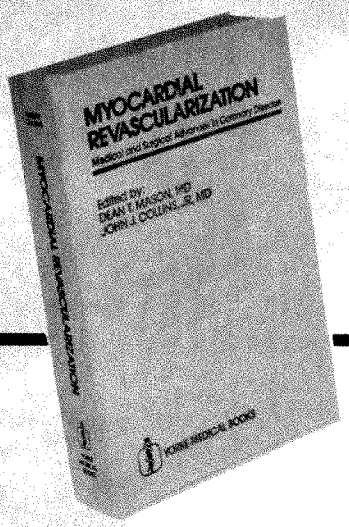

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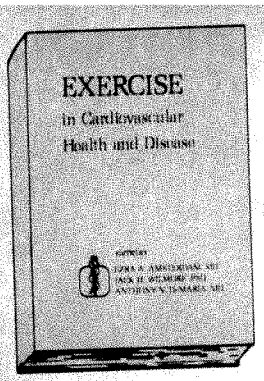

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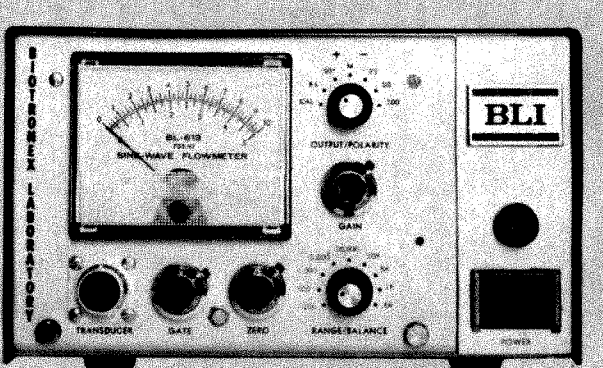

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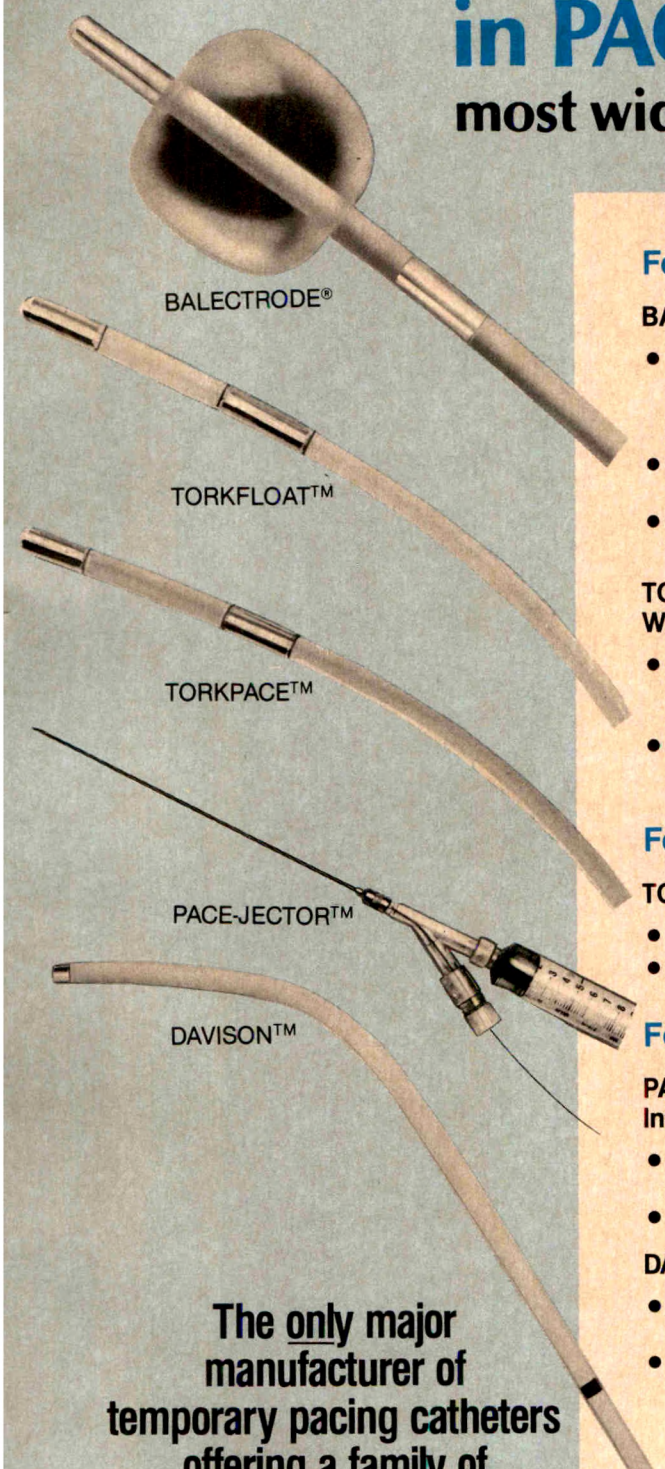

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677 Quantitative Comparison of Extent of Coronary Narrowing and Size of Healed Myocardial Infarct in 33 Necropsy Patients With Clinically Recognized and in 28 Necropsy Patients With Clinically Unrecognized ("Silent") Previous Acute Myocardial Infarction

HENRY SCOTT CABIN and WILLIAM C. ROBERTS

Clinical and necropsy observations are described in 61 patients with a healed transmural myocardial infarction, 33 with and 28 without a clinical history of acute myocardial infarction. Compared with the patients who had clinically recognized acute myocardial infarction, the patients with clinically unrecognized ("silent") infarction had a significantly ($p < 0.05$) higher incidence of diabetes mellitus (43 versus 15%), death from noncardiac causes (39 versus 9%), posterior (inferior) wall infarcts (82 versus 55%), and smaller infarcts (mean size 7 versus 17% of left ventricular wall).

682 Anatomic and Prognostic Implications of an Early Positive Treadmill Test

RICKY M. SCHNEIDER, JOHN F. SEAWORTH, MARY L. DOHRMANN, ROBERT M. LESTER, HARRY R. PHILLIPS, THOMAS M. BASHORE, and JOHN T. BAKER

Eighty men with clinical coronary artery disease were catheterized regardless of symptoms and previous therapy because they had a positive treadmill test in stage I or II of the Bruce protocol. Left main coronary artery stenosis of 50% or greater of the vessel diameter was found in 28% of these patients. Fifty-four patients from this group who did not have left main stenosis of 50% or greater were treated medically. In this subgroup, 85% had 2 or 3 major coronary vessels with 75% or greater stenosis. These patients had a 36 month survival rate of 89.2%. Thus, an early positive treadmill test identifies patients with an increased likelihood of having left main stenosis, even if they have minimal symptoms. After left main stenosis has been excluded by cardiac catheterization, these patients may be treated medically with a low mortality.

689 Effect of Nifedipine on Exercise-Induced Left Ventricular Dysfunction and Myocardial Hypoperfusion in Stable Angina

NADIM M. ZACCA, MARIO VERANI, ROBERT A. CHAHINE, and RICHARD R. MILLER

The present study was designed to assess the effects of nifedipine on left ventricular function at rest and during exercise in 15 patients with coronary artery disease and stable angina pectoris. Myocardial perfusion scintigraphy was also performed in 11 of the 15 patients in an attempt to elucidate the mechanism underlying such effects in these patients. Nifedipine was shown to improve left ventricular performance in general in those patients. It significantly improved the rest as well as the peak exercise ejection fraction. Importantly, it caused no significant deterioration in ejection fraction or in regional wall motion in any patient. In fact, it decreased the deterioration in regional wall motion from rest to peak exercise. In certain patients, nifedipine appeared to improve exercise-induced myocardial perfusion defects.

696 Randomized Double-Blind Comparison of Verapamil and Nifedipine in Chronic Stable Angina

V. BALA SUBRAMANIAN, MICHAEL J. BOWLES, NARDEV SINGH KHURMI, ANTHONY B. DAVIES, and EDWARD B. RAFTERY

The antianginal efficacy of 2 calcium antagonists, verapamil (360 mg/day) and nifedipine (60 mg/day), were compared in a double-blind randomized crossover trial in 32 patients with chronic stable angina. Maximal treadmill exercise testing with on-line computer analysis of the electrocardiogram, 24 hour Holter monitoring using a frequency-modulated cassette tape recorder, and systolic time intervals were the criteria used for evaluating efficacy and safety. Twenty-eight patients completed the trial. Both drugs improved exercise tolerance and other objective variables of ischemia, and the results achieved with verapamil were significantly better than those with nifedipine. Palpitations and angina were reported by 4 patients after taking nifedipine; Holter monitoring revealed episodes of tachycardia associated with S-T depression. Verapamil appears more efficacious and better tolerated in the therapeutic dose range in patients with chronic stable angina.

704 Hemodynamic and Electrophysiologic Effects of Verapamil and Nifedipine in Patients on Propranolol

MICHAEL D. WINNIFORD, ROY V. MARKHAM, BRIAN G. FIRTH, PASCAL NICOD, and L. DAVID HILLIS

The acute effects of intravenous verapamil (0.15 mg/kg to a maximum of 10 mg) or sublingual nifedipine (10 mg) were assessed in patients receiving oral propranolol (234 ± 230 mg/day, mean ± standard deviation). Cardiac output was unchanged by verapamil but increased with nifedipine. Left ventricular dP/dt was reduced only by

Continued on Page A31

the initial antihypertensive dosage of the beta blocker you prescribe...

	recommended initial dosa in hypertension
CORGARD[1] (Nadolol)	40 mg o.d.
TENORMIN[2] (Atenolol)	50 mg o.d.
LOPRESSOR[3] (Metoprolol Tartrate)	50 mg b.i.d.
INDERAL[4] (Propranolol Hydrochloride)	40 mg b.i.d.
BLOCADREN® (Timolol Maleate | MSD)	10 mg b.i.d.

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[4]registered trademark of Ayerst Laboratories

*Cardioprotective dosage—the dosage recommended in the Prescribing Information to reduce the risk of reinfarction or cardiovascular mortality for stabilized patients who have survived the acute phase of an MI

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Only BLOCADREN is presently indicated for the post-MI patient to reduce the risk of reinfarction, and BLOCADREN is the only beta blocker whose dosage has been established through extensive clinical trials to be the same for post-MI as for initial therapy in hypertension. In hypertension the starting dosage is only 10 mg b.i.d. There is only one dosage for prophylactic use in stabilized patients surviving the acute phase of an MI: 10 mg b.i.d.

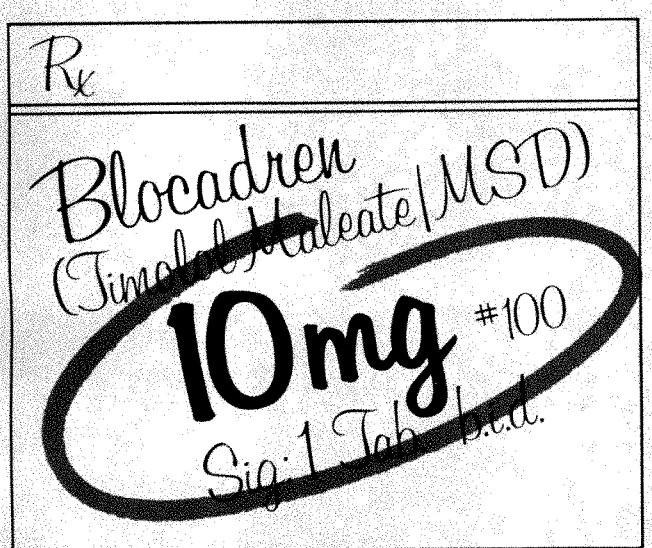
BLOCADREN is contraindicated in patients with: bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see below); cardiogenic shock; and hypersensitivity to this product.

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disea following Abrupt Withdrawal— Hypersensitivity to catecholamines ha been observed in patients withdrawn from beta-blocker therapy; exacerbatic of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronica administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of on to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and othe measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

for initial therapy in hypertensive patients



Usual dosage range:
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Maximum dosage:
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There should be an interval of at least seven days between increases in dosages.

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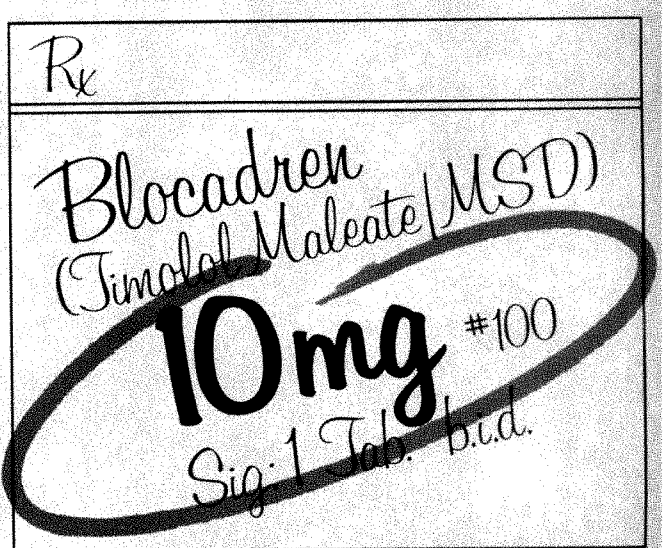

Dosage:
10 mg b.i.d.

Treatment should be initiated within 1 to 4 weeks after infarction.

Data are not available as to whether benefit would ensue if initiated later.

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WARNINGS:

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In Patients without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS:

General: Impaired Hepatic or Renal Function: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Dosing in the Presence of Marked Renal Failure: Marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20-mg doses. Dosing in such patients should therefore be especially cautious.

Drug Interactions: Close observation of the patient is recommended when BLOCADREN is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

Pregnancy—Category C: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n=176) %	Placebo (n=168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
INTEGUMENTARY		
pruritus	1.1	0
NERVOUS SYSTEM		
dizziness	2.3	1.2
vertigo	0.6	0
paresthesia	0.6	0
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta-blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction*		Withdrawal†	
	Timolol (n=945) %	Placebo (n=939) %	Timolol (n=945) %	Placebo (n=939) %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure—Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema—Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

*When an adverse reaction recurred in a patient, it is listed only once.

†Only principal reason for withdrawal in each patient is listed.

These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole*: extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular*: cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive*: gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Endocrine*: hyperglycemia, hypoglycemia; *Integumentary*: rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal*: arthralgia; *Nervous System*: local weakness; *Psychiatric*: depression, nightmares, somnolence, insomnia, nervousness, diminished concentration; *Respiratory*: cough; *Special Senses*: visual disturbances, dry eyes; *Urogenital*: impotence, urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System*: reversible mental depression progressing to catatonia; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular*: intensification of AV block (see CONTRAINDICATIONS); *Gastrointestinal*: mesenteric arterial thrombosis, ischemic colitis; *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Allergic*: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous*: reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

Clinical Laboratory Test Findings: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations.

1082 (DC7117610)

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verapamil. Verapamil reduced the heart rate and increased A-H intervals; in contrast, nifedipine increased heart rate but did not change the A-H interval. The left ventricular ejection fraction was unaltered by verapamil but increased with nifedipine. Thus, when given to patients receiving propranolol, nifedipine improves cardiac output and left ventricular ejection fraction without affecting atrioventricular conduction, whereas verapamil diminished left ventricular contractility and slows atrioventricular conduction. A propranolol-verapamil combination must be used carefully in patients with underlying left ventricular dysfunction or conduction system disease.

711 Long-Term Follow-Up of Verapamil and Nitrate Treatment for Coronary Artery Spasm

S. BENEDICT FREEDMAN, DAVID R. RICHMOND, and DAVID T. KELLY

Thirty-seven patients with coronary artery spasm without significant atherosclerosis were followed-up for a mean of 21 months after the start of verapamil therapy. All had angina at rest, 32 had nocturnal angina, and 13 had a positive exercise test with S-T elevation. Ten had serious arrhythmias, causing syncope in 7. At last review 27 continued on verapamil, 4 nonresponders to verapamil were taking nifedipine, and 16 were taking additional isosorbide dinitrate. Of the 31 on therapy, 21 were asymptomatic and 9 had improved. Six had stopped therapy, 5 of whom remained asymptomatic. Continuation of smoking was positively associated with recurrence of angina on withdrawal of treatment. Long-term treatment of coronary artery spasm with verapamil or nifedipine and isosorbide dinitrate was well tolerated and angina was relieved completely or attacks were markedly reduced. No documented serious arrhythmia, syncopal episodes, myocardial infarction, or death occurred during follow-up.

716 Pharmacokinetics of Verapamil: Experience With a Sustained Intravenous Infusion Regimen

MICHAEL J. REITER, DAVID G. SHAND, LINDA M. AANONSEN, ROBERT WAGONER, ELIZABETH McCARTHY, and EDWARD L. C. PRITCHETT

From the disappearance kinetics of a single intravenous dose of verapamil administered to 9 subjects, a 3 stage intravenous infusion regimen of verapamil was designed to rapidly achieve and maintain a constant plasma verapamil concentration. The regimen consisted of a loading bolus (10 mg over 2 minutes), followed by a 30 minute loading infusion (0.375 mg/min), and finally a maintenance infusion (0.125 mg/min). This regimen was tested in 7 subjects during sinus rhythm for 2 to 12 hours. Maintenance plasma concentration averaged 122 ng/ml and was associated with stable prolongation of the P-R interval, transient and slight decreases in blood pressure and sinus cycle length, and no significant side effects.

722 Variability of Response to Beta-Receptor Blockade for Angina Pectoris in Clinical Trials: A Study of Pindolol

WILLIAM E. HARSTON and GOTTLIEB C. FRIESINGER

Pindolol produced a significant decrease in the double-product and improvement in exercise tolerance in patients with angina pectoris. However, when the same patients were evaluated in a long-term crossover study, there was no clinical improvement over placebo. Patients on placebo had a gradual improvement in exercise tolerance, possibly due to a training effect. Individual patient response to pindolol varied, with some showing clinical improvement and some no improvement despite similar reductions in double-product. Angina occurred at a lower double-product with exercise, suggesting that beta blockade adversely affected other variables of myocardial oxygen demand or decreased coronary blood supply. This study illustrates the difficulties with patient variability and study design that are encountered in studies of beta-blocking agents for angina pectoris.

728 Antiarrhythmic, Antifibrillatory, and Hemodynamic Actions of Bethanidine Sulfate: An Orally Effective Analog of Bretylium for Suppression of Ventricular Tachyarrhythmia

MARVIN B. BACANER and DAVID G. BENDITT

Bethanidine sulfate is a chemical and pharmacologic analog of bretylium tosylate that has virtually identical antifibrillatory and inotropic actions on the heart. Bretylium is the only drug approved by the Food and Drug Administration specifically for the "prophylaxis and treatment of ventricular fibrillation." Unlike bretylium, which is poorly absorbed from the gut and limited to parenteral use, oral bethanidine is absorbed rapidly. Bethanidine was given to 23 patients with recurrent multiple drug refractory ventricular tachycardia and fibrillation. Eighteen patients (78%) had complete suppression of spontaneous or electrophysiologically inducible tachyarrhythmia; 3 patients were improved and 2 had no benefit. In 6 of 9 patients studied by programmed electrophysiologic drug testing, bethanidine completely prevented previously inducible ventricular tachyarrhythmia at the maximal stimulus tested (including 4 extrastimuli and burst-pacing at 10 times threshold). Cardiac output measured in 6 pa-

Continued on Page A32

tients 1 to 2 hours after bethanidine was increased in 4, unchanged in 2, and decreased in 1. Ten patients on long-term therapy with bethanidine and protriptylene (to prevent orthostatic hypotension) have been free of arrhythmia 2 to 26 months.

735 **Continuous Monitoring of Left Ventricular Performance With the Computerized Nuclear Probe During Laryngoscopy and Intubation Before Coronary Artery Bypass Surgery**

ROBERT W. GILES, HARVEY J. BERGER, PAUL G. BARASH, SANJIWAN TARABADKAR, PETER G. MARX, GRAEME L. HAMMOND, ALEXANDER S. GEHA, HILLEL LAKS, and BARRY L. ZARET

Left ventricular performance was monitored serially in 25 patients during laryngoscopy and intubation in the anesthetic induction period before elective coronary artery bypass surgery using the labeled equilibrium blood pool and the computerized nuclear probe. All patients had an immediate decrease in left ventricular ejection fraction accompanying reflex hypertension, and tachycardia during laryngoscopy and endotracheal intubation. The left ventricular ejection fraction was significantly decreased for 3 minutes. Seven patients had no recovery of left ventricular ejection fraction compared with the preintubation value. Ten healthy noncardiac patients undergoing orthopedic surgery had a similar decrease in ejection fraction, but of shorter duration. This study demonstrates that profound decreases in left ventricular performance accompany reflex hypertension and tachycardia occurring during endotracheal intubation, and that some patients with coronary artery disease have a persistent decrease in left ventricular function.

744 **Constrictive Pericarditis as a Complication of Cardiac Surgery: Recognition of an Entity**

MICHAEL A. KUTCHER, SPENCER B. KING III, BENJAMIN N. ALIMURUNG, JOSEPH M. CARVER, and R. BRUCE LOGUE

Eleven patients in whom constrictive pericarditis developed after cardiac surgery are reported on (incidence 0.21%). The pericardium had been left open in all cases. The average time to presentation of pericardial constriction was 82 days after surgery (range 14 to 186). The diagnosis was suspected on clinical and echocardiographic grounds, and confirmed by cardiac catheterization. Three patients eventually responded to medical therapy. Eight patients required a radical pericardiectomy. Constrictive pericarditis may develop as a complication of cardiac surgery in spite of an open pericardium. This entity should be considered in postoperative patients who present with deteriorating cardiac function.

749 **Increased Physical Activity: A Protective Factor Against Heart Attacks in Puerto Rico**

MARIO R. GARCIA-PALMIERI, RAUL COSTAS, Jr., MERCEDES CRUZ-VIDAL, PAUL D. SORLIE, and RICHARD J. HAVLIK

The incidence and potential risk factors of coronary heart disease were assessed in 2,585 rural and 6,208 urban men, aged 45 to 64 years, participating in the Puerto Rico Heart Health Program, a prospective epidemiologic study of coronary heart disease initiated in 1965. An index of daily physical activity and a metabolic equivalent of heaviest activity were estimated from each individual history. Rural men had higher mean levels of overall activity as well as higher levels of heavy activity than urban men. An 8¼ year follow-up study for coronary heart disease other than angina pectoris was analyzed for relationships with physical activity. Significant inverse associations were found for both urban and rural men. Although the physical activity index was inversely associated with most known coronary risk factors, multivariate analyses indicated a significant independent inverse relation with the incidence of coronary heart disease. In Puerto Rico, increased physical activity appears to be a separate protective factor against heart attack.

756 **Inter- and Intraatrial Dissociation During Spontaneous Atrial Flutter: Evidence for a Focal Origin of the Arrhythmia**

PETER L. FRIEDMAN, PEDRO BRUGADA, KARL-HEINZ KUCK, DENIS ROY, JERONIMO FARRE, FRITS W. H. M. BÄR, and HEIN J. J. WELLENS

Electrophysiologic studies in 2 patients with atrial flutter provide evidence that this arrhythmia may be focal in origin, arising in a relatively small area of atrial myocardium. In 1 patient a burst of rapid atrial pacing during atrial flutter precipitated atrial fibrillation in several regions of the atria, while typical atrial flutter persisted in other regions. In another patient a pattern of 3:2 Wenckebach conduction was noted between the left and right atria during atrial flutter. Whether due to focal reentry or triggered automaticity, atrial flutter may be present in some parts of the atria and not others and may even be inapparent in the surface electrocardiogram.

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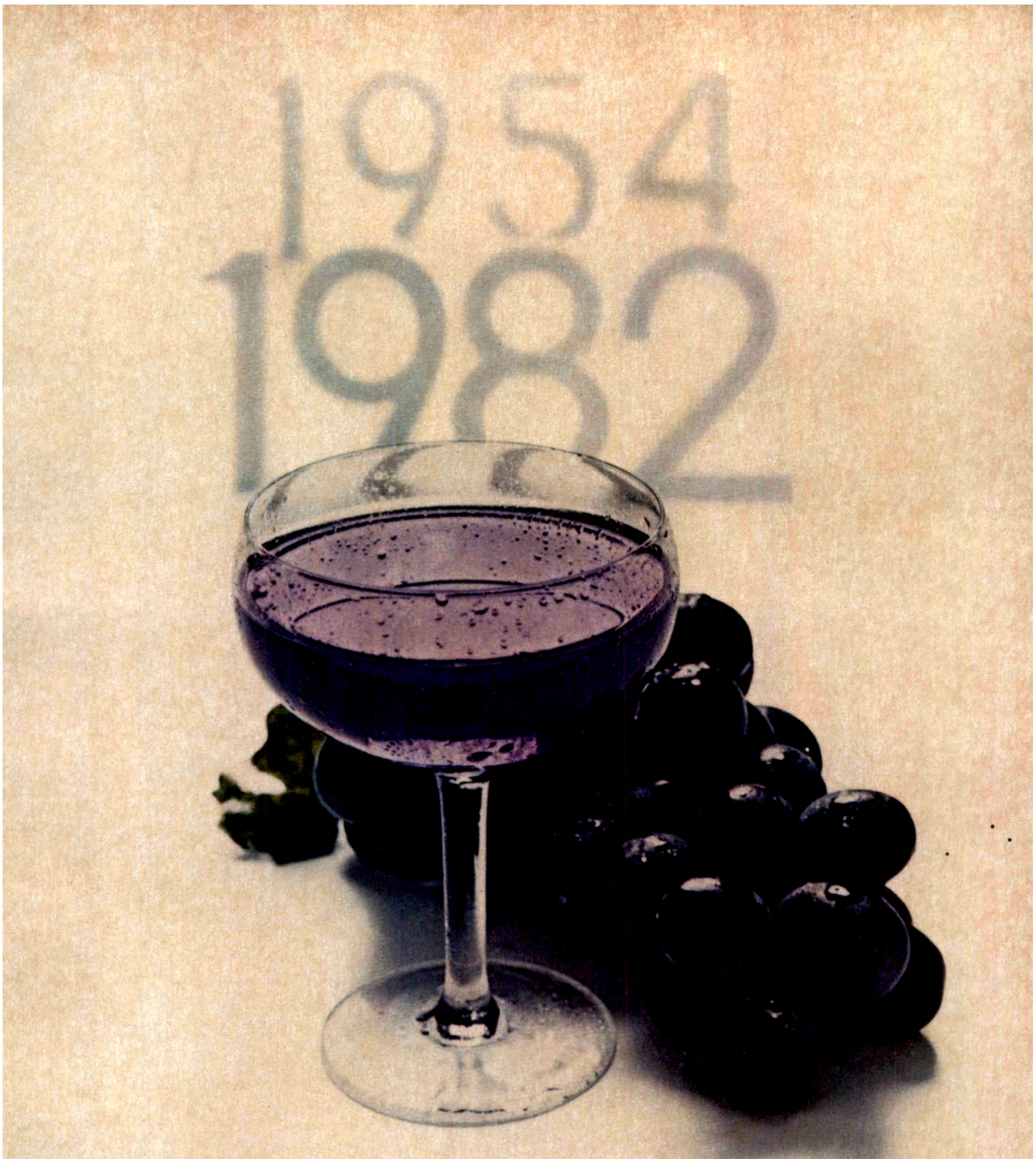

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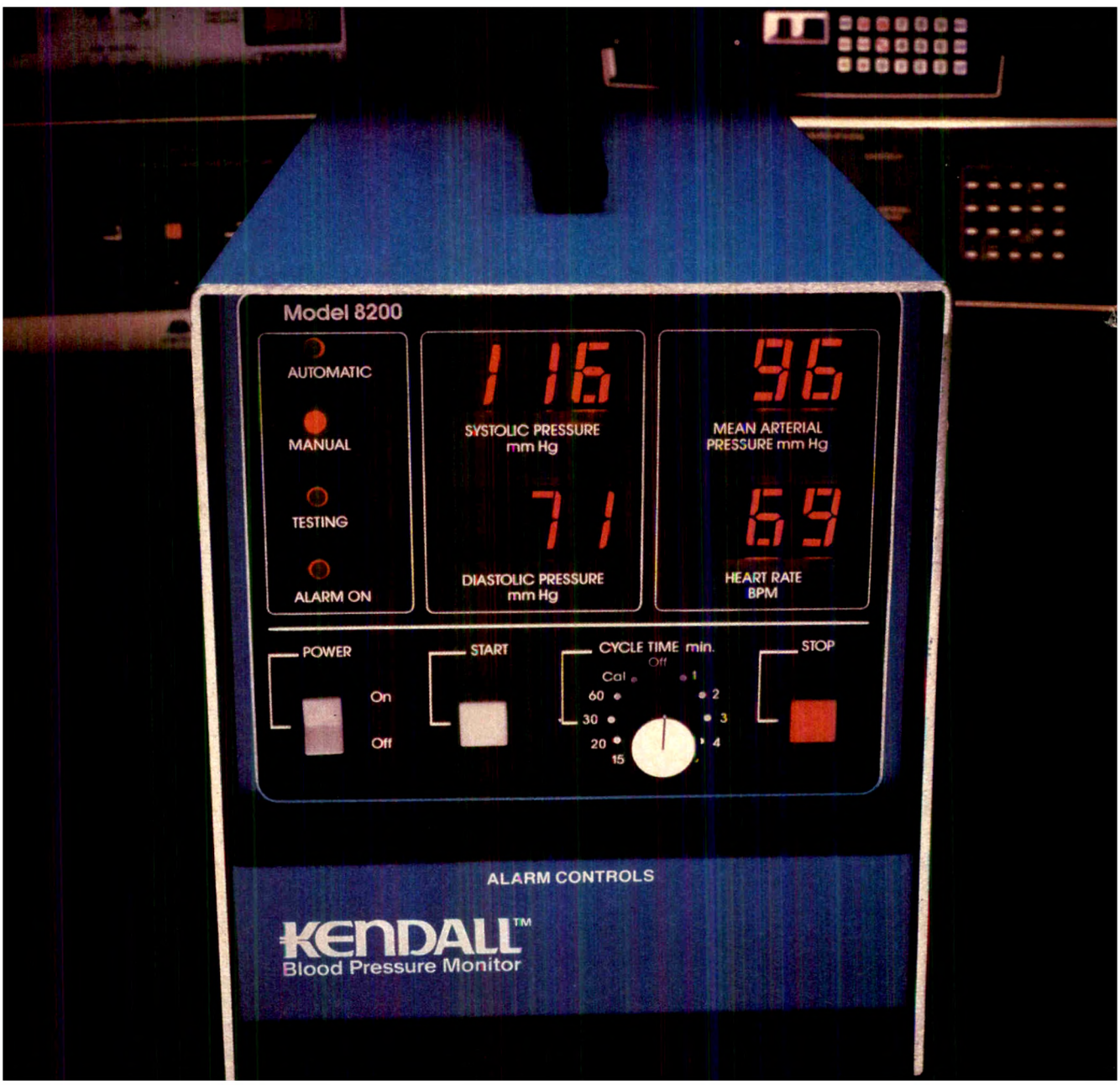
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ALARM ON
116
SYSTOLIC PRESSURE
mm Hg
71
DIASTOLIC PRESSURE
mm Hg
96
MEAN ARTERIAL
PRESSURE mm Hg
69
HEART RATE
BPM
POWER
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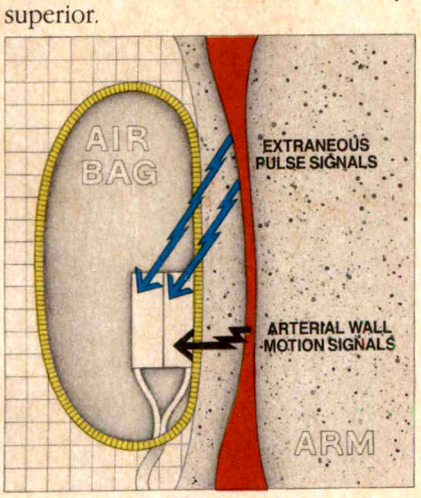

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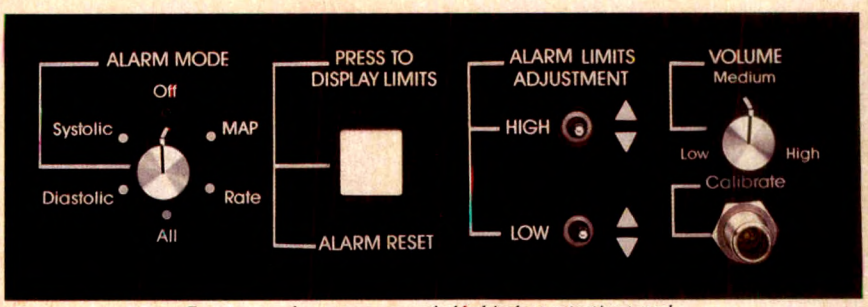

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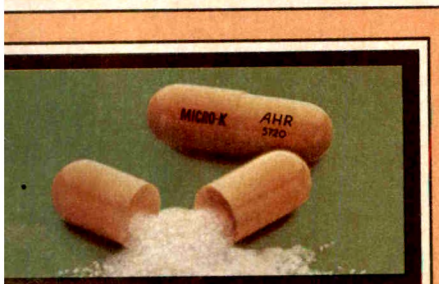

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(Potassium Chloride)

Controlled-Release Extencaps® 8 mEq

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(Potassium Chloride)
Controlled-Release Extencaps® 8 mEq

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- 10,000 individually coated crystals
- Special dispersing agent, to minimize high local concentrations
- Diffusion of liquid KCl over 8-10 hours

Prescribing Information

Description: Micro-K Extencaps are hard gelatin capsules, each containing 600 mg of dispersible small crystalline particles of potassium chloride (equivalent to 8 mEq K). Each particle is microencapsulated with a polymeric coating which allows for controlled release of potassium and chloride ions over an eight- to ten-hour period. The dispersibility of the microcapsules and the controlled release of ions are intended to minimize the likelihood of high localized concentrations of potassium chloride and resultant mucosal ulceration within the gastrointestinal tract.

The polymeric coating forming the microcapsules functions as a water-permeable membrane. Fluids pass through the membrane and gradually dissolve the potassium chloride within the microcapsules. The resulting potassium chloride solution slowly diffuses outward through the membrane.

Actions: Potassium ion is the principal intracellular cation of most body tissues. Potassium ions participate in a number of essential physiological processes, including the maintenance of intracellular tonicity, the transmission of nerve impulses, the contraction of cardiac, skeletal, and smooth muscle and the maintenance of normal renal function.

Potassium depletion may occur whenever the rate of potassium loss through renal excretion and/or loss from the gastrointestinal tract exceeds the rate of potassium intake. Such depletion usually develops slowly as a consequence of prolonged therapy with oral diuretics, primary or secondary hyperaldosteronism, diabetic ketoacidosis, severe diarrhea, or inadequate replacement of potassium in patients on prolonged parenteral nutrition. Potassium depletion due to these causes is usually accompanied by a concomitant deficiency of chloride and is manifested by hypokalemia and metabolic alkalosis. Potassium depletion may produce weakness, fatigue, disturbances of cardiac rhythm (primarily ectopic beats), prominent U-waves in the electrocardiogram, and in advanced cases, flaccid paralysis and/or impaired ability to concentrate urine.

Potassium depletion associated with metabolic alkalosis is managed by correcting the fundamental causes of the deficiency whenever possible and administering supplemental potassium chloride, in the form of high potassium food or potassium chloride solution, capsules or tablets. In rare circumstances (e.g., patients with renal tubular acidosis) potassium depletion may be associated with metabolic acidosis and hyperchloremia. In such patients potassium replacement should be accomplished with potassium salts other than the chloride, such as potassium bicarbonate, potassium citrate, or potassium acetate.

INDICATIONS: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases, supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: *Hyperkalemia.* In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.

The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustments.

Interaction with Potassium-Sparing Diuretics. Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions. Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths, in addition to upper gastrointestinal bleeding. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation.

Micro-K Extencaps contain microcapsules which disperse upon dissolution of the hard gelatin capsule. The microcapsules are formulated to provide a controlled release of potassium chloride. The dispersibility of the microcapsules and the controlled release of ions from the microcapsules are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of KCl into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated KCl), but have not eliminated them. The frequency of GI lesions with Micro-K Extencaps is, at present, unknown. Micro-K Extencaps should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis. Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and may be minimized by taking the dose with meals or by reducing the dose.

Intestinal bleeding, ulceration, perforation and obstruction have been reported in patients treated with solid dosage forms of potassium salts and may occur with Micro-K Extencaps (see Contraindications and Warnings).

One of the most severe adverse effects of potassium supplementation is hyperkalemia (see Contraindications, Warnings, and Overdosage).

Skin rash has been reported rarely with potassium preparations.

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiogram changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following: (1) elimination of foods and medications containing potassium and of potassium-sparing diuretics; (2) intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml; (3) correction of acidosis, if present, with intravenous sodium bicarbonate; (4) use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

Dosage and Administration: The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient, but typically is in the range of 2 to 3 Micro-K Extencaps per day (16 to 24 mEq K) for the prevention of hypokalemia and 5 to 12 Micro-K Extencaps (40 to 96 mEq K) or more per day for the treatment of potassium depletion. If more than 2 Micro-K Extencaps are prescribed per day, the total daily dosage should be divided into two or more separate doses.

How Supplied: Pale orange capsules (Extencaps), each containing 600 mg microencapsulated potassium chloride (equivalent to 8 mEq K) in bottles of 100 (NDC 0031-5720-63), and 500 (NDC 0031-5720-70) and Dis-Co® unit dose packs of 100 (NDC 0031-5720-64).

Animal Toxicology: The ulcerogenic potential of microencapsulated KCl was studied in anesthetized cats by direct applications on exteriorized gastric mucosa. The microcapsules of KCl were found to be non-ulcerogenic and significantly less irritating than wax-matrix tablets and 20% solution of KCl.

In groups of monkeys (up to 8 monkeys per group) receiving different formulations of potassium chloride at equivalent daily dosage (2400 mg KCl) for four and one-half days, Micro-K Extencaps showed no tendency to cause intestinal ulceration (similar to liquid KCl and a wax-matrix preparation but in contrast to an enteric-coated KCl tablet) and minimal gastric irritation (less than a wax-matrix preparation).

July 1980

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Pharmaceutical Division
Richmond, Virginia 23261-6609

CONTENTS

762 **Echocardiographic Features of Carcinoid Heart Disease**

JOHN A. CALLAHAN, EDMUND M. WROBLEWSKI, GUY S. REEDER, WILLIAM D. EDWARDS, JAMES B. SEWARD, and ABDUL J. TAJIK

The records of the Mayo Clinic patients with known carcinoid syndrome in whom echocardiographic studies had been done were reviewed. Nineteen patients had M-mode and 2-dimensional echocardiographic examinations, and 1 patient had an M-mode examination only. Of the 20 patients, 8 had no evidence by echocardiogram of carcinoid heart disease; 2 had changes in the tricuspid valve echogram suggestive of early carcinoid heart disease, and the other 10 patients had the following distinctive echocardiographic findings: (1) a pattern of right ventricular volume overload (enlarged right ventricle with abnormal septal motion); (2) abnormal right-sided valves, including (a) a striking appearance of the tricuspid valve, the leaflets appearing thickened, retracted, and fixed in a semiopen position throughout the cardiac cycle, and (b) thickened, retracted pulmonary cusp valves, when visualized; and (3) the left-sided valves and chambers rarely involved. These echocardiographic features are distinctive of advanced carcinoid heart disease and correlate closely with pathologic findings.

PEDIATRIC CARDIOLOGY

769 **Exercise Electrocardiogram, Blood Pressure, and Working Capacity in Young Patients With Valvular or Discrete Subvalvular Aortic Stenosis**

FREDERICK W. JAMES, DAVID C. SCHWARTZ, SAMUEL KAPLAN, and STEVE P. SPILKIN

Electrocardiographic changes, blood pressure, and working capacity (total work) were recorded during an upright cycle exercise test in 65 children and young adults with valvular or discrete subvalvular aortic stenosis. Exercise-induced S-T depression increased in frequency and amplitude with increasing pressure gradient across the left ventricular outflow tract. Mean total work and peak exercise systolic pressure were significantly lower in the patients than in control subjects. An exercise profile consisting of S-T depression of 2 mm or more and markedly decreased total work and exercise systolic pressure was characteristic of patients with a resting left ventricular-aortic systolic gradient of 70 mm Hg or greater. At least 2 or more components of this exercise profile occurred in 20% of patients with a gradient less than 70 mm Hg. Exercise testing reveals serious abnormalities in patients otherwise classified as having trivial or moderate aortic stenosis.

776 **Mechanism of Acquired Right Ventricular Outflow Tract Obstruction in Patients With Ventricular Septal Defect: An Angiocardiographic Study**

GIACOMO PONGIGLIONE, ROBERT M. FREEDOM, DAVID COOK, and RICHARD D. ROWE

Right ventricular outflow tract obstruction can complicate the natural history of patients with isolated ventricular septal defect. Although numerous pathologic mechanisms may be responsible for this phenomenon, it is less clear what the frequency is of each of these mechanisms in any cohort of patients studied in a single institution. Twenty patients were identified who had isolated ventricular septal defect from 1970 to 1981 and who acquired a right ventricular outflow tract gradient of 25 mm Hg or greater. They ranged in age at the initial catheterization investigation from 4 days to 23 months and on subsequent study from 13 months to 8 years. Angiographically, 2 mechanisms were implicated in the 20 patients. Hypertrophy of right ventricular anomalous muscle bundles was identified in 19 of the 20 while hypertrophy of a maligned infundibular septum (that is, classic tetralogy type) was identified in only 1 patient. These data indicate that acquired right ventricular outflow tract obstruction is rarely of the classic tetralogy type.

781 **Surgical Repair of Congenitally Corrected Transposition of the Great Arteries: Results and Follow-Up**

BETAU HWANG, FREDERICK BOWMAN, JAMES MALM, and EHUD KRONGRAD

Eighteen patients with congenitally corrected transposition of the great arteries had open heart surgery for repair of intracardiac defects. Fourteen patients (78%) are alive (mean follow-up 4.5 years). Postoperative hemodynamic compromise was directly related to identifiable residual defects such as atrioventricular valve insufficiency, residual septal defect, or pulmonary conduit stenosis. Eight of 18 patients required more than 1 open heart operation. No patient had primary ventricular dysfunction. None of the last 11 patients had complete heart block, but surgical injury to the bundle branches was common. Improved knowledge of the precise location of the atrioventricular conduction system in congenitally corrected transposition resulted in a marked decrease in atrioventricular block. Also, in the absence of postoperative residual defects longevity and quality of life may improve considerably, but many patients may require a second operation.

Continued on Page A43

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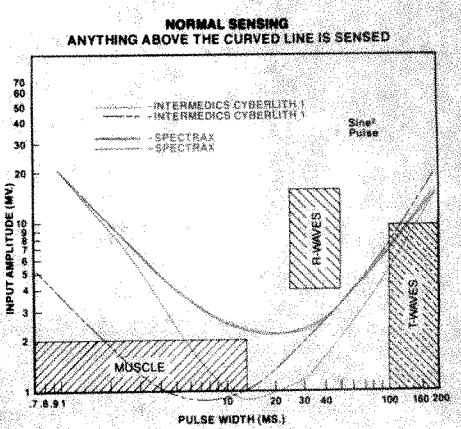

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[1]for more information, see PACE, vol. 5, No. 1, pages 1-37.

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Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses). An atrial pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation disorders but with intact, functioning A-V conduction systems. Cardiac pacing using an implantable A-V sequential pulse generator is for long-term therapeutic control of heart rate in patients where restoration of A-V synchrony is indicated to improve cardiac output or to protect against arrhythmias related to sequence of cardiac impulse propagation.

Contraindications

There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.

Warnings

Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. See the specific precautions and warnings in the technical manuals included with the pulse generator.

Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

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786 Left and Right Ventricular Adaptation to Right Ventricular Overload Before and After Surgical Repa of Tetralogy of Fallot

PETER E. LANGE, DIETRICH G. W. ONNASCH, ALEXANDER BERNHARD, and PAUL H. HEINTZEN

Angiographic volume data were obtained for the left (n = 43) and the right (n = 56) ventricle in tetralogy of F before and after surgical repair. The preoperatively decreased ($p < 0.01$) left ventricular ejection fraction di improve postoperatively, even if excellent results were achieved. A certain functional reserve, however pears to be preserved, since the ejection fraction did not decrease further with increasing volume loads d a residual ventricular septal defect. Postoperatively the right ventricular ejection fraction was reduced si cantly ($p < 0.01$) compared with normal even without significant outflow tract obstruction or additional vo load. The further decrease in ejection fraction with increasing volume loads due to pulmonary insufficienc sidual ventricular septal defect, or both suggests a loss of functional reserve. Attempts to minimize right ve ular volume load after surgical repair of tetralogy of Fallot appear advisable.

795 Early Assessment of Hemodynamic Status After Repair of Tetralogy of Fallot: A Comparison of 24 Hour (Intensive Care Unit) and 1 Year Postoperative Data in 98 Patients

PETER LANG, CARL W. CHIPMAN, HAROLD SIDEN, ROBERTA G. WILLIAMS, WILLIAM I. NORWOOD, and ALDO R. CASTANEDA

Hemodynamic data obtained in the intensive care unit, immediately after repair of tetralogy of Fallot, were pared with measurements obtained at 1 year postoperative catheterization in 98 infants and children. Inte care unit measurement of pulmonary arterial oxygen saturation is valuable for determining the presence c sence of significant left-to-right shunts after repair of tetralogy of Fallot and should be considered an adjur patient management. Intensive care unit measurement of right ventricular outflow tract gradient identifie tients with a significant gradient but is not highly sensitive.

800 Pediatric Cardiac Catheterization With Same-Day Discharge

J. DEANE WALDMAN, TERRANCE S. YOUNG, STANLEY J. PAPPELBAUM, SEARLE W. TURNER, STANLEY E. KIRKPATRICK, and LILY M. GEORGE

Experience with cardiac catheterization in 233 children without overnight hospital stay (same-day disch was evaluated. In 232 children, no problems occurred after hospital discharge; 1 child required readmissi psoas tendinitis after retrograde aortography. Same-day discharge was safely applied regardless of age, di sis, systemic heparinization, use of large-bore sheaths, retrograde arterial catheterization, or cineangiogr Hospital costs were reduced 29% compared with the standard 42 hour stay. Same-day discharge offers th lowing advantages: (1) improved medical care, (2) reduced medical costs, and (3) elimination of time-pre in training and teaching as well as therapeutic decision-making. Critical factors in success are coordinat multiple health care professionals and physician judgment of the patient's clinical status. We speculate reassessment of other hospital-oriented procedures may foster the development of methods to improve m care, reduce cost, or both.

804 Compression of Intrapulmonary Bronchi by Abnormally Branching Pulmonary Arteries Associated With Absent Pulmonary Valves

MARLENE RABINOVITCH, STAFFORD GRADY, IVAN DAVID, RICHARD VAN PRAAGH, URSULA SAUER, KONRAD BUHLMEYER, ALDO R. CASTANEDA, and LYNNE REID *with the technical assistance of* DONNA K. SILVA

In 3 patients with absent pulmonary valve syndrome and absent ductus arteriosis, the lungs were injecte analyzed postmortem using morphometric techniques. Two patients had tetralogy of Fallot and 1 had D-tra sition of the great arteries, the latter being the first autopsy-proved case of absent pulmonary valve with tra sition. In addition to the expected dilatation of the central pulmonary arteries and compression of the mai bronchi, postmortem pulmonary artery arteriography revealed a bizarre pattern of hilar branching. Instead gle segmental arteries, tufts of arteries arose which entwined and compressed the intrapulmonary bron 1 case the number of bronchial generations was decreased and in 1 other case alveolar multiplication w verely impaired. Our data may therefore explain why, in some patients with absent pulmonary valve sync relief of compression of the mainstem bronchus alone does not appreciably alleviate or reverse severe re tory disease.

Continued on Page A48

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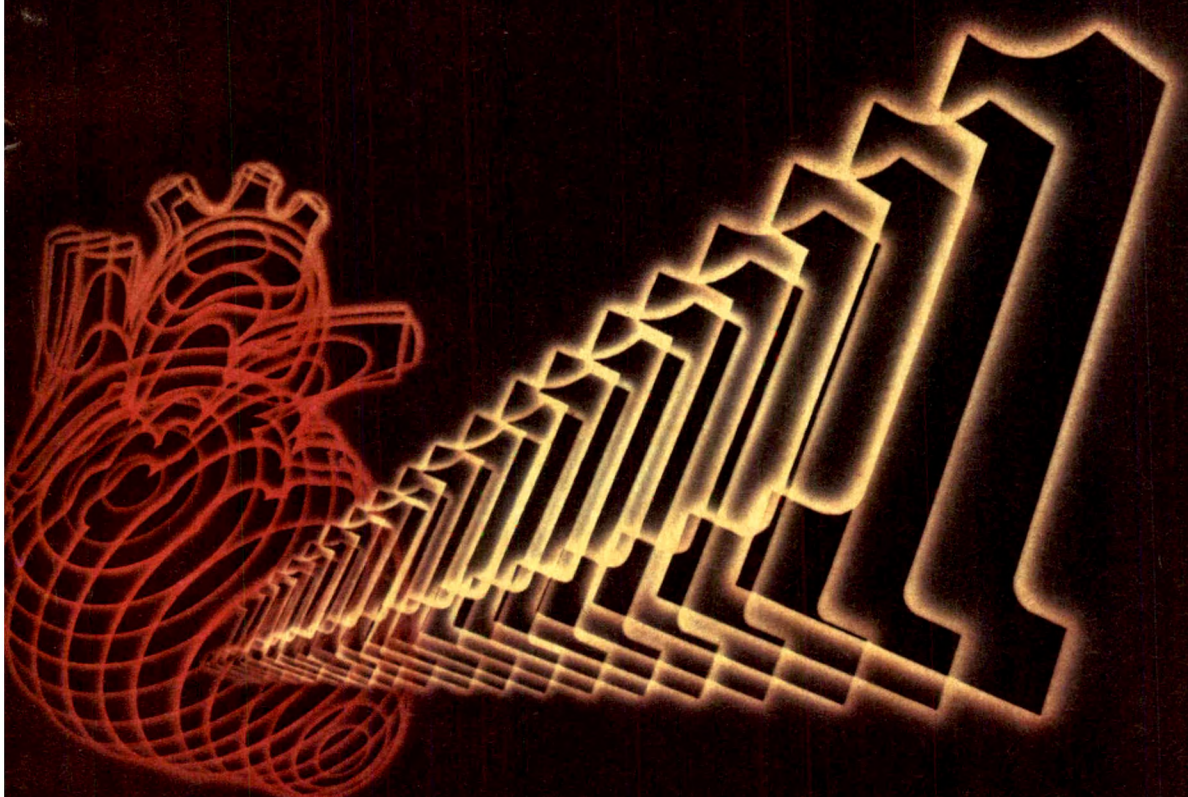

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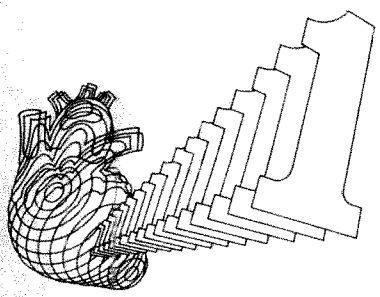

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DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta$_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a beta$_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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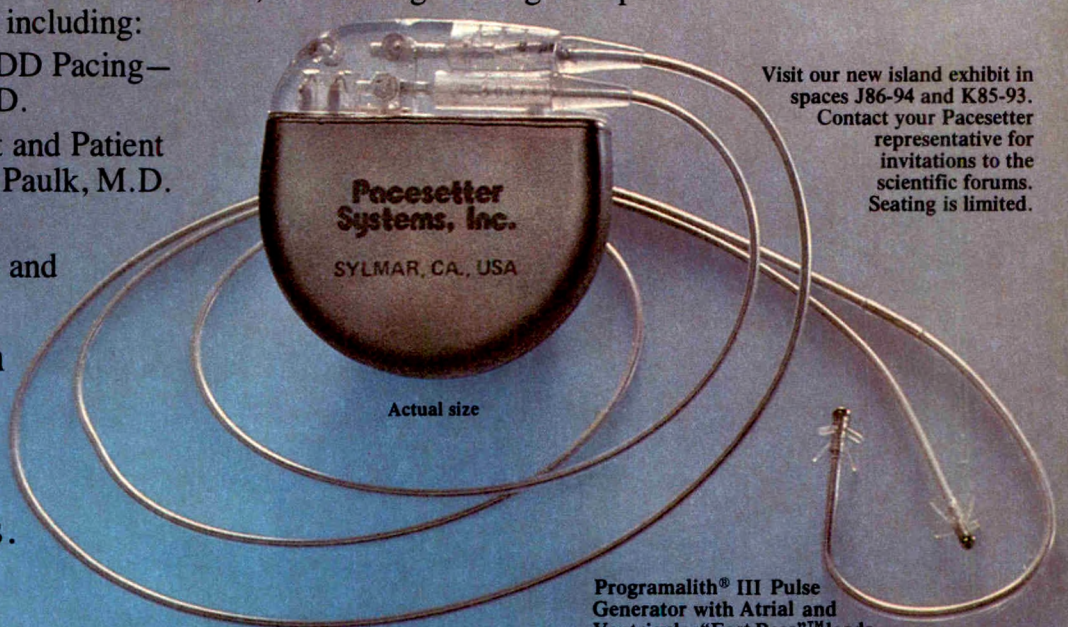

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CONTENTS

814 Two-Dimensional Echocardiographic Identification of Pulmonary Artery Branch Stenosis

DAVID D. TINKER, NAVIN C. NANDA, J. PETER HARRIS, and JAMES A. MANNING

The use of real-time, 2-dimensional echocardiography in the detection of pulmonary artery stenosis is described in 10 patients with congenital heart disease, all of whom had angiographically documented pulmonary artery stenosis. The merits of various transducer positions in detecting this lesion and the difficulties associated with diagnosing pulmonary branch stenosis by echocardiography are discussed.

EXPERIMENTAL STUDIES

821 Ventricular Performance and Biochemical Alteration of Regional Ischemic Myocardium After Reperfusion in the Pig

MARVIN L. MURPHY, CHUN FU PENG, JAMES J. KANE, and KARL D. STRAUB

This study, using an animal model, evaluates regional left ventricular wall thickness, analyzes metabolic and biochemical changes, and examines tissue hemorrhage during 15, 30, and 120 minutes of myocardial ischemia, each followed by 120 minutes of reperfusion. Reperfusion after 15 minutes of ischemia showed nearly normal ventricular wall thickening and motion, intact metabolic and biochemical function, and no tissue hemorrhage. However, reperfusion after 30 and 120 minutes of ischemia was associated with ventricular wall thickening and failure to resume systolic and diastolic wall motion. Furthermore, adverse metabolic and biochemical alterations and myocardial hemorrhaging increased with the duration of ischemia. These findings suggest critical myocardial damage occurring between 15 and 30 minutes of ischemia in an animal model without preexisting coronary collateral circulation. The observed metabolic and biochemical changes are consistent with irreversible cell membrane defects allowing Ca^{2+} accumulation and adversely affecting diastolic relaxation and systolic thickening.

829 Effect of Intraaortic Balloon Counterpulsation on Regional Myocardial Blood Flow and Oxygen Consumption in the Presence of Coronary Artery Stenosis: Observations in an Awake Animal Model

HENRY GEWIRTZ, WILLIAM OHLEY, DAVID O. WILLIAMS, YING SUN, and ALBERT S. MOST

In this study the mechanism by which arterial counterpulsation relieves myocardial ischemia in patients with unstable angina pectoris was examined. Studies were conducted in closed-chest conscious pigs instrumented with severe (82% reduction in luminal diameter) coronary artery stenosis. Hemodynamics, regional myocardial blood flow (microspheres), and oxygen consumption were measured at control, after 15 to 20 minutes of intraaortic balloon pumping, and at second control. In response to pumping, there was no change (versus control) in endocardial blood flow distal to the stenosis. Epicardial flow and myocardial oxygen consumption distal to the stenosis decreased in response to intraaortic balloon pumping. The data support the hypothesis that intraortic balloon pumping relieves myocardial ischemia in patients with unstable angina pectoris primarily by reducing myocardial oxygen demand rather than by increasing oxygen supply.

838 Detection of Ischemic Myocardium in Vivo Through the Chest Wall by Quantitative Ultrasonic Tissue Characterization

RANDOLPH D. COHEN, JACK G. MOTTLEY, JAMES G. MILLER, PETER B. KURNICK, and BURTON E. SOBEL

Quantitative analysis of ultrasound is potentially valuable for noninvasive differentiation of specific types of cardiac disease, if the effects of intervening tissue can be compensated for. Accordingly, to characterize the quantitative effects of the chest wall on ultrasonic signal backscattered by ischemic and normal myocardium, frequency-dependent backscatter was measured in dogs both through the closed chest and with the chest open, directly from the myocardium. Closed-chest and open-chest measurements were repeated after ligation of the left anterior descending coronary artery. Closed-chest data were compensated by correcting for the average slope of the attenuation-frequency function of chest wall. Compensated closed-chest measurements correlated with epicardial measurements. Differentiation of normal from ischemic myocardium was achieved with both closed- and open-chest measurements ($p < 0.005$). These results suggest that tissue characterization through the chest wall may be a practical approach for noninvasive detection of intrinsic properties of normal and diseased myocardium.

Continued on Page A54

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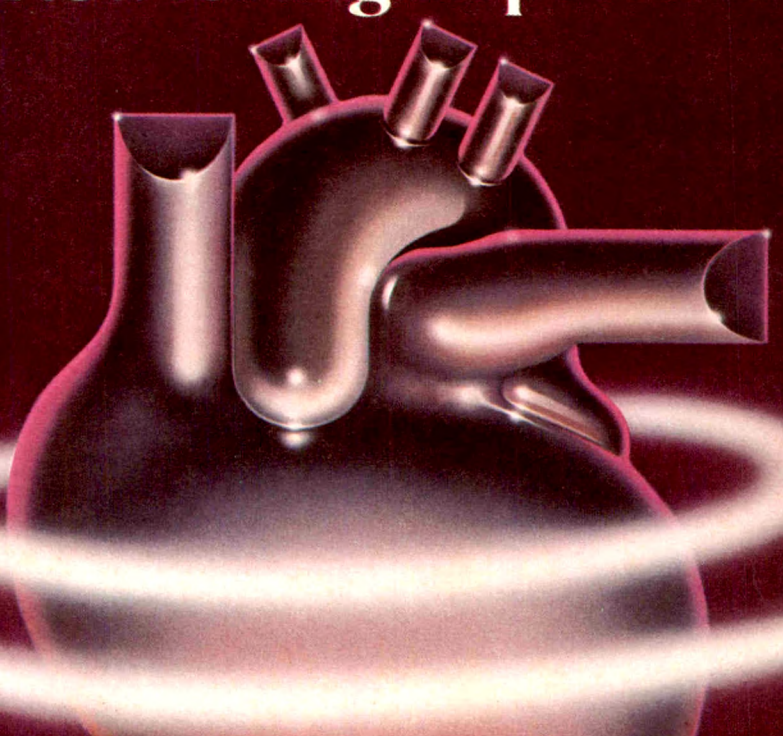

Now for angina pectoris

ISOPTIN® TABLETS (verapamil HCl/Knoll)

In angina of effort:

Isoptin decreases myocardial oxygen demand and improves exercise tolerance

By decreasing peripheral vascular resistance and decreasing cardiac afterload, Isoptin decreases the workload of the heart and the amount of oxygen consumed by the myocardium. This action accounts for the significant improvement in exercise tolerance and reduction in angina attacks that Isoptin produces in patients with classic angina of effort.

An agent with two major antianginal actions

In angina at rest:

Isoptin dilates the coronary arteries and prevents coronary vasospasm

While beta blockers may cause coronary vasoconstriction, Isoptin has been shown to prevent spasm and to dilate both normal and atherosclerotic coronary arteries. This action accounts for the significant reduction in the frequency of both anginal attacks and ischemic ECG events that Isoptin produces in patients with unstable (preinfarction, crescendo) or Prinzmetal's angina.

Isoptin has proved highly effective in all forms of angina.

In double-blind, crossover studies of angina of effort, patients exercised significantly longer when on Isoptin than on propranolol—42–72% longer on Isoptin (360–480 mg/day) and 30–42% longer on propranolol (240–320 mg/day), compared to placebo.[1-3] It is likely that patients who enter a clinical trial for a new drug have found available therapy unsatisfactory. In one study, for example, patients had been titrated to maximum tolerated doses of propranolol, but were still experiencing effort-induced angina.[2] It is therefore likely that the patient population of these studies was relatively refractory to propranolol, and further studies are required before a conclusion can be drawn from these data.

In a single-blind, crossover study of unstable (preinfarction, crescendo) angina, Isoptin (400 mg/day) produced a highly significant reduction in transient ischemic ECG events and nitroglycerin consumption, while propranolol (300 mg/day) did not differ significantly from placebo.[4] In Prinzmetal's variant angina, Isoptin has also proved highly effective.[5]

Please see last page of this advertisement for brief summary of prescribing information.

ISOPTIN® TABLETS (verapamil HCl/Knoll)

Isoptin improves the oxygen balance of the heart in both angina of effort and angina at rest.

Marked therapeutic effects with infrequent serious side effects

In most patients, including those with organic cardiac disease, the negative inotropic action of Isoptin is countered by reduction of afterload, and cardiac index is usually not reduced. Isoptin does not alter total serum calcium levels.

Adverse reaction to Isoptin	Incidence in 1166 patients
Constipation	6.3%
Dizziness	3.6%
Hypotension	2.9%
Headache	1.8%
Peripheral edema	1.7%
Nausea	1.6%
Bradycardia (HR < 50 beats/min)	1.1%
Fatigue	1.1%
CHF or pulmonary edema	0.9%
AV block (third degree)	0.8%

Why Isoptin, and not a beta blocker?

In addition to its high degree of efficacy in both major types of angina, Isoptin requires no special caution in patients with asthma, COPD, diabetes or peripheral vascular disease, including Raynaud's Disease.

Careful patient selection is important

Isoptin is contraindicated in severe left ventricular dysfunction, sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker), hypotension or cardiogenic shock and second- or third-degree AV block.

Concomitant use with other cardioactive drugs warrants caution

In view of limited experience with concomitant use of Isoptin and beta blockers, Isoptin should be used alone, if possible. If combination therapy is used, it should involve close surveillance of vital signs and clinical status, periodic reassessment of the need for concomitant treatment with the beta blocker, and should probably be avoided in patients with AV conduction abnormalities or depressed left ventricular function. Since concomitant use of calcium antagonists and digoxin increases serum digoxin levels, maintenance digoxin dosage should be reduced and the patient carefully monitored. Until further data are obtained, disopyramide phosphate should not be administered within 48 hours before or 24 hours after Isoptin; and in patients with hypertrophic cardiomyopathy, quinidine should not be administered concomitantly with Isoptin.

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Please see next page for brief summary of prescribing information.

ISOPTIN® TABLETS
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80 mg and 120 mg

Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction <30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before ISOPTIN is used. ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild, and controlled by decrease in ISOPTIN dose). Occasional elevations of liver enzymes have been reported; patients receiving ISOPTIN should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (e.g., W-P-W or L-G-L syndromes) may develop a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema, and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with ISOPTIN. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patient carefully monitored. ISOPTIN may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C :* There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, maculae, and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in 80 mg and 120 mg sugar-coated tablets. July 1982 2068

References: **1.** Frishman WH, Klein NA, Strom JA, et al: *Circulation* 65 (suppl I): 151-159, 1982. **2.** Leon MB, Rosing DR, Bonow RO, et al: *Am J Cardiol* 48:131-139, 1981. **3.** Bala Subramanian V, Bowles MJ, Davies AB, et al: *Am J Cardiol* 49:125-132, 1982. **4.** Data on file, Knoll Pharmaceutical Company. **5.** Johnson SM, Mauritson DF, Willerson JT, et al: *N Engl J Med* 304:862-866, 1981. 2041R

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CONTENTS

844 Increased R-Wave Amplitude Induced by Acute Myocardial Ischemia in the Dog: A Predictor of Malignant Ventricular Arrhythmias

DANIEL DAVID, ERIC L. MICHELSON, MASAHITO NAITO, MARK SCHAFFENBURG, and LEONARD S. DREIFUS

The ability of an increase in R-wave amplitude to predict the occurrence of malignant ventricular arrhythmia was evaluated in 17 dogs during experimental acute myocardial ischemia. Dogs underwent temporary 15 minute ligation of the left anterior descending artery and, after recovery, ligation of the circumflex coronary artery. During left anterior descending coronary artery ligation, 12 dogs (71%) showed no R-wave increase and no arrhythmia; 5 (29%) developed ventricular arrhythmia, but only 2 of the 5 (40%) had R-wave increases. During circumflex ligation 13 dogs (76%) had both R-wave increases and arrhythmia; 4 (24%) had no arrhythmia, and 3 of the 4 (75%) also had no increase in R-wave amplitude. In dogs with both arrhythmia and R-wave increases, R-wave changes preceded the onset of arrhythmia by a mean of 1 minute 27 seconds. Overall, R-wave increases were highly sensitive (83%), specific (94%), and predictive (94%) for the occurrence of ventricular arrhythmia during acute myocardial ischemia.

849 Ibuprofen-Mediated Infarct Size Reduction: Effects on Regional Myocardial Function in Canine Myocardial Infarction

PHILIP C. KIRLIN, JOSEPH L. ROMSON, BERTRAM PITT, GERALD D. ABRAMS, M. ANTHONY SCHORK, and BENEDICT R. LUCCHESI

Normal, marginal, and ischemic zone regional myocardial contractile function was measured by sonomicrometer crystals in canine myocardial infarction. Regional function was measured in anesthesized dogs after 90 minute left circumflex coronary occlusion and in conscious, unsedated animals 48 and 72 hours after reperfusion through a critical stenosis. Animals received either intravenous ibuprofen or vehicle as a control. Ibruprofen (5.36 mg/kg/h) significantly reduced histochemically determined infarct size at 72 hours but did not improve regional contractile function in normal, marginal, or central ischemic regions at the end of the 90 minute occlusion or after 48 or 72 hours of reperfusion. Inotropic reserve at 72 hours was also unchanged. The assessment of changes in regional myocardial contractile function after infarct size reduction with ibuprofen or other agents may require prolonged observation.

857 Protective Effects on Isolated Hearts With Developing Infarction: Slow Channel Blockade by Diltiazem Versus Beta-Adrenoceptor Antagonism by Metoprolol

CHRISTIAN W. HAMM, FRANCIS T. THANDROYEN, and LIONEL H. OPIE

This study was designed to assess and compare the effects of the beta-receptor antagonist metoprolol with those of the calcium channel inhibitor diltiazem on cellular damage and mechanical function in the isolated working rat heart subjected to coronary artery ligation. The highest concentrations of both agents that could be tolerated in this preparation were compared: diltiazem, 4×10^{-7} *M*; and metoprolol, 10^{-4} *M*. These concentrations were equally effective in reducing enzyme release, which was taken as an index of cellular damage, and preserved high energy phosphate content in the infarcting myocardium. However, the 2 agents exhibited opposite effects on coronary flow rates and mechanical function. Compared with diltiazem, metoprolol reduced total coronary flow, cardiac output, and left ventricular work and efficiency immediately after coronary artery ligation. Diltiazem, however, appeared to have a favorable influence on the mechanical performance of the isolated heart compared with untreated control hearts during the 60 minute duration of regional myocardial ischemia. These benefits were similarly apparent when the hearts were paced to the rate of control hearts. The presumed mechanism was coronary vasodilation, because afterload increased as left ventricular power production increased. These results suggest that further evaluation of diltiazem in other preparations is warranted.

864 Inhibition of Hypoxic Pulmonary Vasoconstriction by Nifedipine

THOMAS KENNEDY and WARREN SUMMER

The effect of nifedipine on the relation between pulmonary arterial pressure and blood flow during normoxia (PAO_2 = 200 mm Hg) and hypoxia (PAO_2 = 50 mm Hg) was evaluated in ventilated pig lungs perfused in situ with the animal's own blood. Nifedipine, given as a 0.1 or 10 μg/kg bolus into the pulmonary artery, caused a dose-dependent reduction of pulmonary vasoconstriction caused by hypoxia. We conclude that nifedipine is a potent pulmonary vasodilator which markedly attenuates hypoxic pulmonary vasoconstriction.

Continued on Page A59

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1. **Has the patient been taking Persantine long enough?** It often takes two to three months for clinical improvement to manifest itself.
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Tablets of 25, 50 and 75 mg

Persantine®

The experienced dipyridamole

INDICATIONS—Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension. Persantine tablets, 25 mg, contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. The incidence of sensitivity is generally low, but frequently seen in patients with aspirin hypersensitivity.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

Tablets of 25, 50 and 75 mg

For complete details, please see the full prescribing information.

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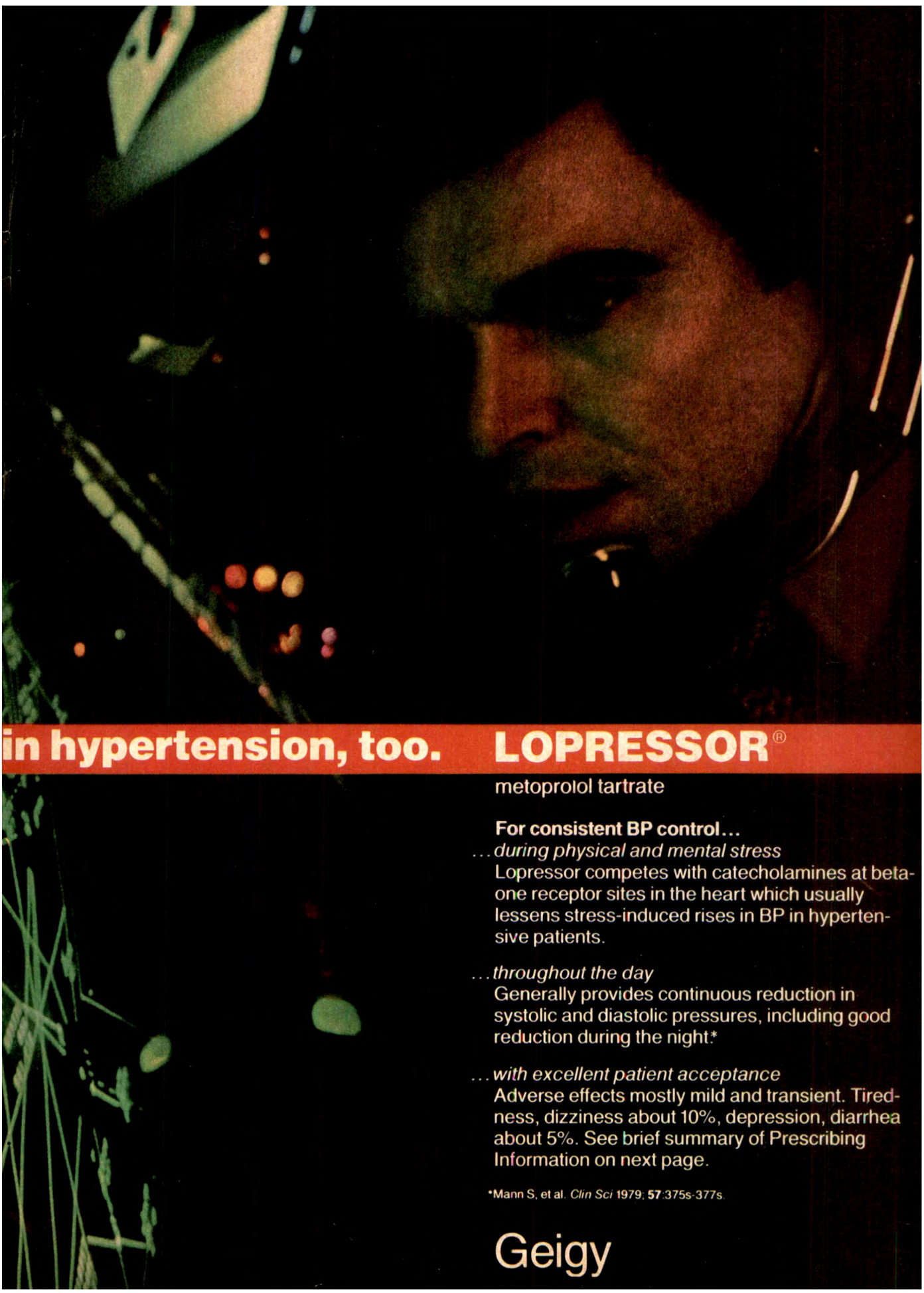

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For consistent BP control...

...during physical and mental stress
Lopressor competes with catecholamines at beta-one receptor sites in the heart which usually lessens stress-induced rises in BP in hypertensive patients.

...throughout the day
Generally provides continuous reduction in systolic and diastolic pressures, including good reduction during the night.*

...with excellent patient acceptance
Adverse effects mostly mild and transient. Tiredness, dizziness about 10%, depression, diarrhea about 5%. See brief summary of Prescribing Information on next page.

*Mann S, et al. *Clin Sci* 1979; **57**:375s-377s.

Geigy

metoprolol tartrate

An antihypertensive beta-blocking agent — Tablets of 50 mg; Tablets of 100 mg

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.
Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).
Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.
In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.
Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.
Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**
Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.
Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.
Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.
Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.
Impaired Hepatic or Renal Function: The drug should be used with caution in patients with impaired hepatic or renal function.
Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.
Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.
Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.
Usage in Children: Safety and effectiveness in children have not been established.
Adverse Reactions Most adverse effects have been mild and transient.
Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.
Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**
Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**
Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.
Allergic: Pruritus has occurred in less than 1 of 100 patients.
Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients. The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.
Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.
Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.
Cardiovascular: Intensification of AV block (see **Contraindications**).
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.
Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.
Miscellaneous: Reversible alopecia.
Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.
Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.
This drug should be stored at controlled room temperature and protected from moisture.
How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.
Store at controlled room temperature and protect from moisture.
Dispense in tight, light-resistant container (USP).

C80-82 (12/80)

Consult complete product literature before prescribing.

GEIGY Pharmaceuticals
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Geigy

336-3610-A

CONTENTS

869 Effects of Angiographic Contrast Medium on Isolated Canine Coronary Arteries

HECTOR LARDANI, GUSTAVO RINALDI, and HORACIO CINGOLANI

A widely used angiographic dye elicited marked relaxation in isolated canine coronary arteries previously contracted by either high potassium or norepinephrine. This dose-dependent effect was not prevented either by beta blockade or by an increase in osmolarity similar to the one produced by the dye. This relaxant action and the one elicited by nitroglycerin were additive. Changes in cyclic guanosine or adenosine monophosphate could not account for the relaxant effect of the contrast medium.

874 Digital Intravenous Ventriculography: Analysis and Validation of Wall Thickness Changes During Ischemia and Inotropic Stimulation in Dogs

ROBERT A. SLUTSKY, KENNETH H. GERBER, and CHARLES B. HIGGINS,
with the technical assistance of FRANK H. HAIGLER and FRED G. WERNER

Regional ventricular wall thickness was assessed in anesthesized dogs using digital intravenous ventriculography in a control state, after subtotal and total coronary occlusion, and after the administration of isoproterenol. These measures of wall thickness correlated well with simultaneous measurements made by sonomicrometers placed in the base and distal wall of the ventricle. Thickening was found asymmetric, being greater as the distal wall and apex were approached. These relations were maintained during ischemia and inotropic stimulation. We conclude that digital intravenous ventriculography can be used to assess changes in wall thickness with a high degree of accuracy in dogs.

SYMPOSIUM ON VERAPAMIL THERAPY FOR ANGINA PECTORIS

MILTON PACKER, Guest Editor, and WILLIAM H. FRISHMAN, Guest Co-Editor

881 Verapamil Therapy for Stable and Unstable Angina Pectoris: Calcium Channel Antagonists in Perspective

MILTON PACKER and WILLIAM H. FRISHMAN

This symposium reviews the evidence concerning the therapeutic application of verapamil in patients with angina pectoris. Because of the increasing number of calcium antagonists being developed for clinical use, physicians are faced with the question of which drug to choose. Since available agents appear to be of comparable efficacy, it is likely that the choice of a drug in an individual patient will be determined more by which drug is better tolerated than by which agent is more effective. Verapamil appears to cause adverse reactions less frequently than does nifedipine, but nifedipine is often preferred because it is thought to possess less potential to depress cardiac function and interact with beta-blockers. However, both agents may interact with beta-blockers and both may depress cardiac performance in patients with compromised ventricular function; no comparative studies in the same patients have been performed. Since beta-blockers have an established role in the prophylaxis of future cardiac events in patients with recent myocardial infarction, the critical question concerning the choice of a calcium antagonist remains the relative safety and effectiveness of verapamil versus nifedipine in patients already treated with beta-blocking agents. The answer to this question awaits the results of future clinical trials.

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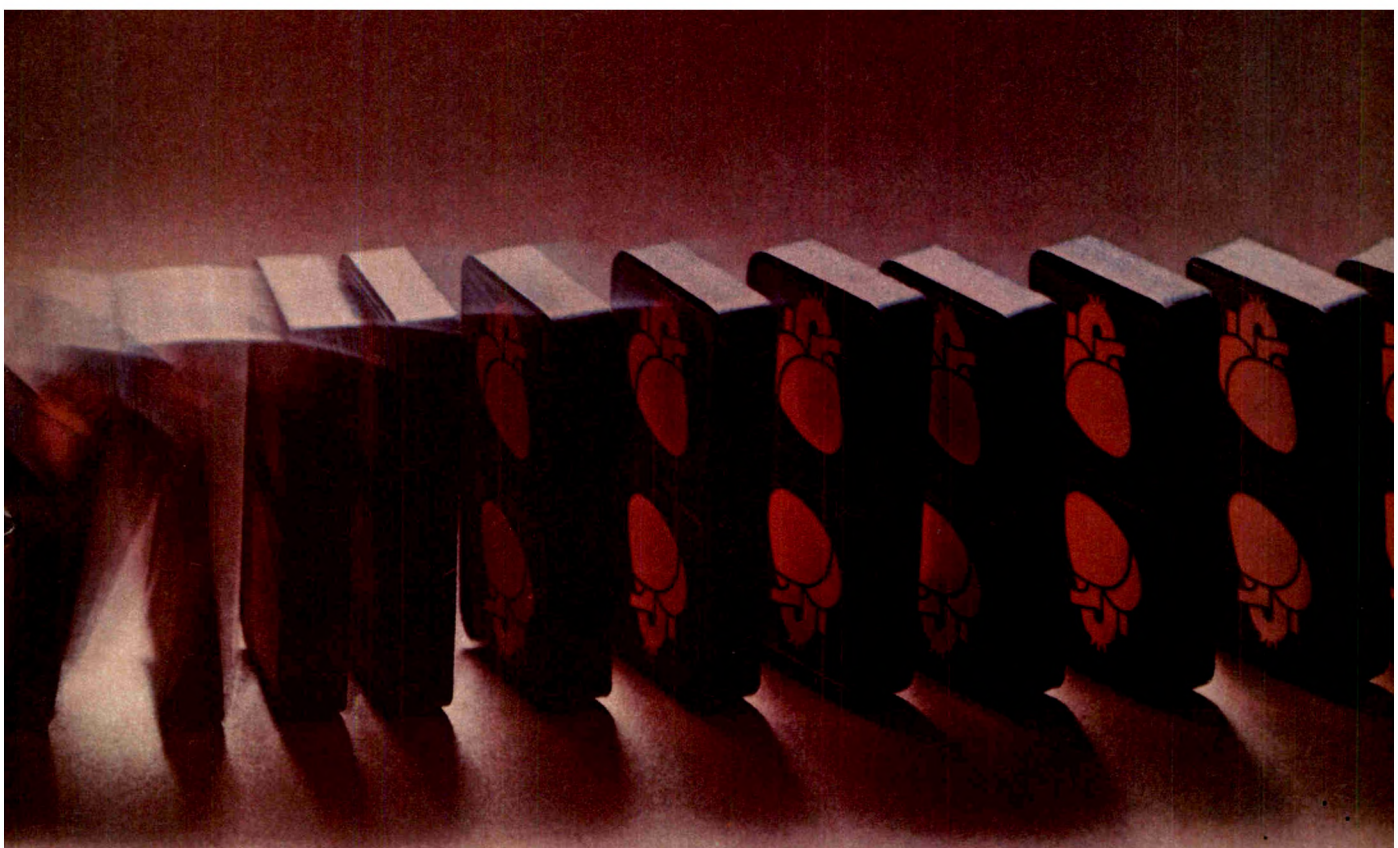
BECAUSE ONE THING CAN LEAD



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Please see next page for Brief Summary of Prescribing Information.

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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
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BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

CONTRAINDICATIONS

1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless it is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: In congestive heart failure, inhibition with beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In patients already receiving digitalis, propranolol may reduce the positive inotropic action of digitalis and may have an additive depressant effect on AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, in rare instances, cardiac failure has developed during propranolol therapy. At the first sign of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and observed closely. a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Give special consideration to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol should be withdrawn slowly, since abrupt withdrawal may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta-blockade impairs the ability of the heart to respond to reflex stimuli. Except in pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery. In case of emergency surgery, the effects of propranolol can be reversed by administration of beta-receptor agonists such as isoproterenol or levarterenol, but such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), administer with caution, since propranolol may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in patients with labile diabetes. A precipitous elevation of blood pressure may accompany hypoglycemic attacks.

USE IN PREGNANCY: Safe use in human pregnancy not established. Embryotoxic effects have been seen in animals at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if propranolol is administered, since it may occasionally produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

Observe laboratory parameters at regular intervals. Use with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta-blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

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TABLETS

--Each hexagonal-shaped, orange, scored tablet is embossed with an "I" and imprinted with "INDERAL 10," contains 10 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0421-81) and 1,000 (NDC 0046-0421-91). Also in unit dose package of 100 (NDC 0046-0421-99).

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Store at room temperature (approximately 25° C).

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8015/882

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CONTENTS

PART I: PHARMACOLOGIC AND HEMODYNAMIC ACTIONS AND INTERACTIONS

886 Pharmacologic and Hemodynamic Mechanisms Underlying the Antianginal Actions of Verapamil

BRAMAH N. SINGH, CHRISTOPHER Y. C. CHEW, MARTIN A. JOSEPHSON, and MILTON PACKER

In patients with a severely reduced ventricular ejection fraction and high ventricular filling pressure, verapamil may produce clinical and hemodynamic deterioration. Computer-assisted angiographic analysis has shown that verapamil dilates normal as well as narrowed epicardial coronary vessels and reverses ergonovine- and sympathetically provoked coronary vasoconstriction. Intravenous verapamil administration reduces coronary arterial resistance and enhances coronary sinus flow with variable effects on myocardial oxygen consumption. The drug prevents the ischemic consequences of angina produced by atrial pacing; after verapamil administration, pacing-induced lactate production is lessened, and ischemia-related decreases in left ventricular ejection fraction are prevented. During chronic therapy, the effects of verapamil on regional and global ventricular function are similar to those of propranolol during supine bicycle exercise. However, verapamil has a significantly smaller effect on the rate-pressure product at rest and during exercise; this suggests that its antianginal mechanism of action, unlike that of beta-blockers, may not be related solely to a reduction in oxygen demand. These data indicate that the mechanisms underlying the antianginal effects of verapamil are complex and are likely to be multifactorial.

894 Verapamil and Digoxin: Their Respective Effects on Atrial Fibrillation and Their Interaction

HERMAN O. KLEIN and ELIESER KAPLINSKY

Although digitalis has long been used in the management of patients with atrial fibrillation, it does not block the excessive increase in ventricular rate which occurs in such patients during mild exercise; in contrast, this inappropriate response is effectively blocked by verapamil. During regular sinus rhythm, atrioventricular (AV) node works well as a *delaying* structure (the P-R interval), and the ventricular rate is a function of the sinus rate only. However, in atrial fibrillation, the AV node has to adopt the role of a *filter* for numerous wave fronts of activity, a function it fulfills poorly, especially during the enhanced sympathetic responses and decreased vagal tone that accompany exercise. In patients with atrial fibrillation, during exercise these autonomic alterations override the vagal effects of digitalis on the AV node, but verapamil remains effective by virtue of its direct action on the slow channel ionic fluxes within the AV nodal cells. The beneficial effect of verapamil on ventricular rate is accompanied by a significant improvement in maximal exercise capacity in patients with atrial fibrillation receiving long-term oral verapamil therapy; thus, it appears superior to digoxin in the treatment of chronic atrial fibrillation.

903 Hemodynamic and Clinical Effects of Combined Verapamil and Propranolol Therapy in Angina Pectoris

MILTON PACKER, MARTIN B. LEON, ROBERT O. BONOW, JOSHUA KIEVAL, DOUGLAS R. ROSING, and V. BALA SUBRAMANIAN

Because of their common negative chronotropic and inotropic effects combined therapy with beta-adrenergic blocking drugs and calcium channel antagonists has long been feared to produce synergistic cardiodepressant effects. To evaluate whether such fears are justified when such therapy is used in patients with angina pectoris, 5 hemodynamic and clinical studies were conducted. These studies indicate that in patients with preserved ventricular function treated with low or moderate doses of propranolol, verapamil produces little change in cardiac performance; this was not significantly different from the effects seen with verapamil in the absence of beta blockade. In patients receiving high doses of propranolol, verapamil produced modest but significant cardiodepressant effects; these could be avoided by withdrawal of propranolol for 24 hours. Adverse reactions when they occurred appeared primarily hemodynamic rather than electrophysiologic in nature. Short-term (48 hours) and long-term (4 weeks) randomized controlled trials demonstrated that combined therapy with verapamil and propranolol was superior not only to placebo but also to the responses observed with either drug used alone.

Continued on Page A67

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Adjustable Atrial Refractory Periods	Maintains full DDD function while avoiding synchronization with retrograde conduction.
Automatic DDD Mode	Allows A-V synchrony to be maintained for maximum hemodynamic benefit.
Four Programmable A-V Delays	Optimizes ventricular filling.

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Cordis Sequicor Technical Information.

Sequicor, Model 233D Programmable Parameters

Modes	DDD, DVI, DAD, VDD, VAT,VVI, DOO, VET,* VOO
Minimum Pacing Rate, (Interval)	50 (1200), 60 (1000), 70 (857), 80 (750)
Maximum Pacing Rate (Interval)	100 (600), 130 (461), 160 (375), 180 (333)
Atrial Sensitivity, (mV)	0.8, 1.5, 7.0, OFF
Ventricular Sensitivity, (mV)	0.8, 1.5, 2.5, OFF
Atrial Output Pulse Duration, (ms)	OFF, 0.5, 1.0, 1.5,
Ventricular Output Pulse Duration, (ms)	0.5, 1.0, 1.5, 2.0,
A/V Delay (ms) †	80, 120, 165, 250
Atrial Tachycardia Response	Fall Back, 2:1 Block
Fall Back Rate (Interval)	55 (1.090), 65 (932), 75 (800), 85 (706)

Sequicor Nonprogrammable Parameters

Output Current mA		Output Voltage	Pace Limit
Atrial	5.5	4.2	195 ppm
Ventricular	5.5	4.2	195 ppm

Other Specifications

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Sequicor Refractory Periods

Atrial Tachycardia Response	Maximum Rate	Total Atrial Refractory	Total Ventricular Refractory	A/V Programmed Delay†	Total Atrial Refractory Following the Ventricle Pulse
2:1 Block	100 ppm	600 ms	302 ms	80 ms	520 ms
				120	480
				165	435
				250	350
	130 ppm	461 ms	302 ms	80 ms	381 ms
				120	341
				165	296
				250	211
	160 ppm	375 ms	302 ms	80 ms	295 ms
				120	255
				165	210
				250	125
	180 ppm	333 ms	302 ms	80 ms	253 ms
				120	213
				165	168
				250	83
Any Fall Back Rate	Any Maximum Rate	305 ms	302 ms	80 ms	225 ms
				120	185
				165	140
				250	55

* VET – Ventricular overdrive (ventricles externally triggered)
† During ventricular overdrive (VET), A-V delay = 6 to 20 ms.

Important Information

Indications
The Cordis Model 233D Sequicor θ (Theta) pacer is a two-channel pacer intended for permanent, two-chamber cardiac pacing.

Adverse Effects
The following list includes a number of complications related to pacer therapy that have been reported in the medical literature. Noninvasive techniques for assessing and managing such complications are available to the physician. Malfunctions occur randomly and may occur at any time after implantation.

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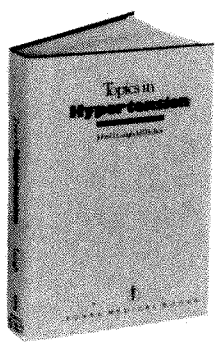

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913 **Verapamil Therapy for Prinzmetal's Variant Angina: Comparison With Placebo and Nifedipine**

MICHAEL D. WINNIFORD, STACEY M. JOHNSON, DAVID R. MAURITSON, JAMES S. RELLAS, GREGORY A. REDISH, JAMES T. WILLERSON, and L. DAVID HILLIS

This study was performed to assess the efficacy and safety of verapamil in patients with variant angina and to compare verapamil and nifedipine in such patients. In 27 patients, placebo and verapamil were administered in a long-term, randomized, double-blind study of 9 months' duration. In comparison with placebo, verapamil reduced the frequency of angina, nitroglycerin use, transient episodes of electrocardiographic S-T segment deviation (as assessed by 2-channel Holter monitoring), and hospitalizations required for clinical instability. Subsequently, 23 of the patients were treated with nifedipine in a nonblinded fashion for 2 months, and this agent exerted a beneficial effect similar to that of verapamil. Finally, gated equilibrium blood pool scintigraphy, performed in 10 patients at rest and during exercise during treatment with placebo, verapamil, and nifedipine, demonstrated that neither calcium antagonist caused a deterioration of left ventricular performance. It is concluded that long-term oral verapamil and nifedipine are each superior to placebo and are of similar efficacy in patients with variant angina, and tha neither agent adversely influences left ventricular performance in patients with relatively normal left ventricular function.

919 **Verapamil Therapy for Unstable Angina Pectoris: Review of Double-Blind Placebo-Controlled Randomized Clinical Trials**

JAWAHAR MEHTA and C. RICHARD CONTI

The effectiveness of verapamil in the management of patients with unstable angina pectoris associated with obstructive coronary artery disease was evaluated in 2 double-blind placebo-controlled randomized clinical trials. In the first study, verapamil was compared with placebo using alternating 48 hour treatment periods in a multiple crossover protocol. Verapamil was superior to placebo in abolishing symptomatic and asymptomatic ischemic episodes; there were 127 ischemic events during treatment with placebo but only 27 episodes during therapy with verapamil ($p < 0.006$). In the second study, verapamil and placebo were compared using a double-blind randomized parallel design, in which the choice of drug was altered and the doses administered were increased according to the individual responses. Verapamil reduced anginal attacks in 12 of 13 patients, but placebo was effective in only 1 of 6 ($p < 0.025$); verapamil reduced daily anginal attacks from 3.2 to 0.6/day ($p < 0.01$). These studies show that verapamil is highly effective in the short-term management of patients with unstable angina secondary to coronary artery disease.

923 **Verapamil Versus Propranolol for Angina at Rest**

OBERDAN PARODI, IGNAZIO SIMONETTI, ANTONIO L'ABBATE, and ATTILIO MASERI

The results of 3 clinical trials comparing the effectiveness of verapamil and propranolol in patients with angina at rest are reviewed. In 17 patients enrolled in a randomized triple-crossover study, verapamil was superior to propranolol in preventing ergonovine-induced coronary artery spasm ($p < 0.001$). In 18 patients with angina at rest evaluated in a double-blind crossover study, both verapamil and propranolol reduced the number of episodes of angina at rest (from 3.0 to 1.7/day with propranolol [$p < 0.05$] and to 0.2/day with verapamil [$p < 0.001$]); the degree of improvement with verapamil was superior to that seen with propranolol ($p < 0.005$). In 10 patients with angina at rest evaluated in a single-blind multiple crossover trial which assessed symptomatic and asymptomatic ischemia, the number of ischemic events was reduced significantly by verapamil (5 ± 1 episodes/48 hours) but not by placebo or propranolol (25 ± 3 and 23 ± 3 episodes/48 hours, respectively). These studies confirm the effectiveness of verapamil in the management of patients with angina at rest; in contrast, the effectiveness of propranolol in this syndrome appears comparable to that of placebo.

SPECIAL DEPARTMENTS

929 **Letters**

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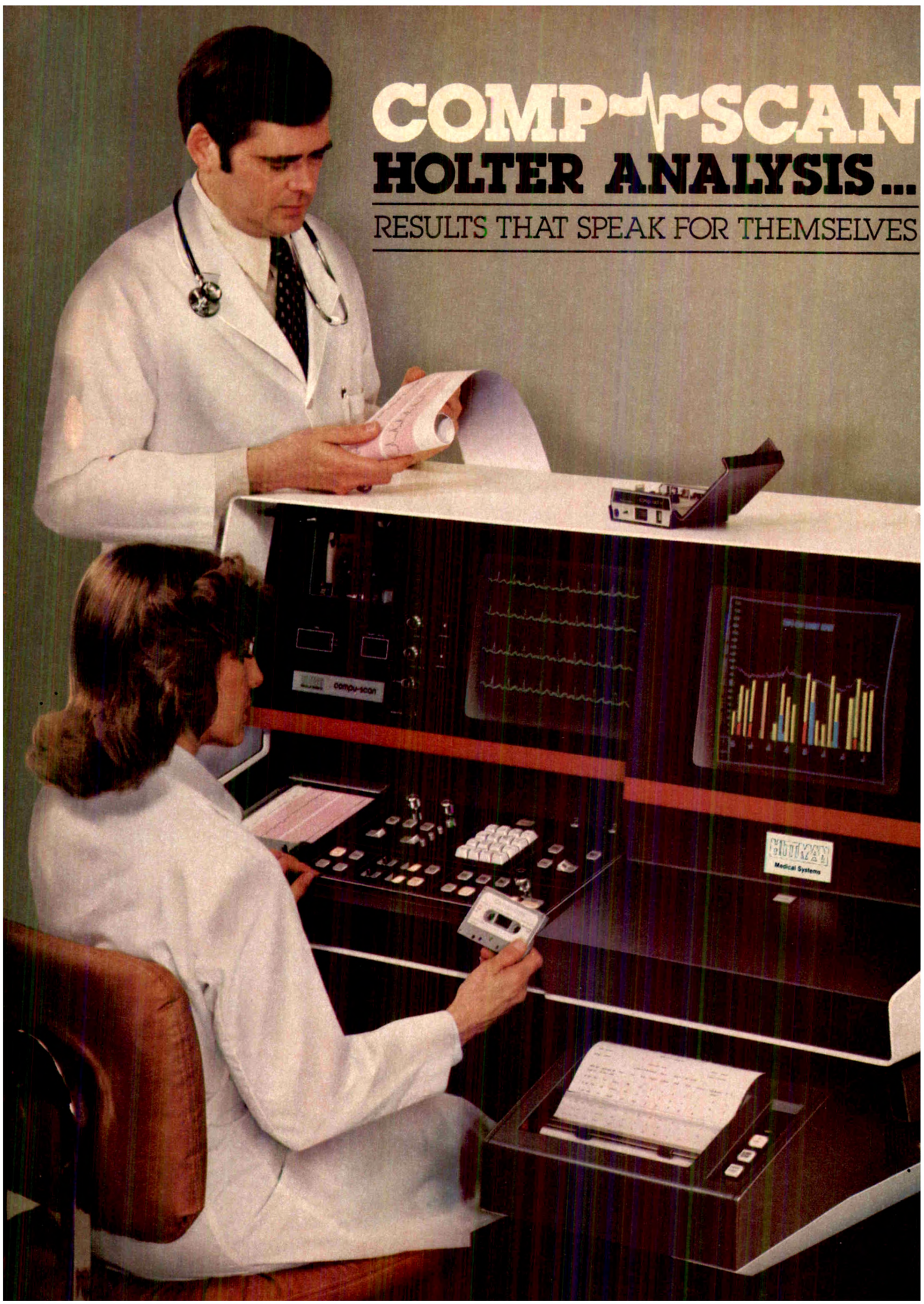
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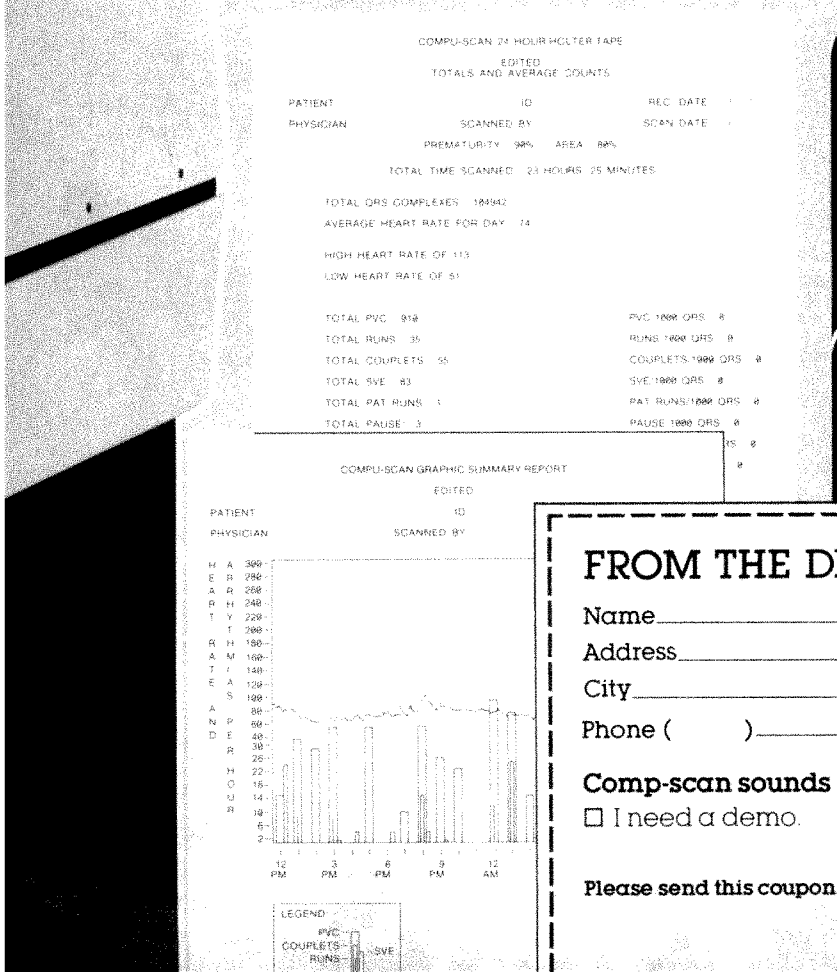

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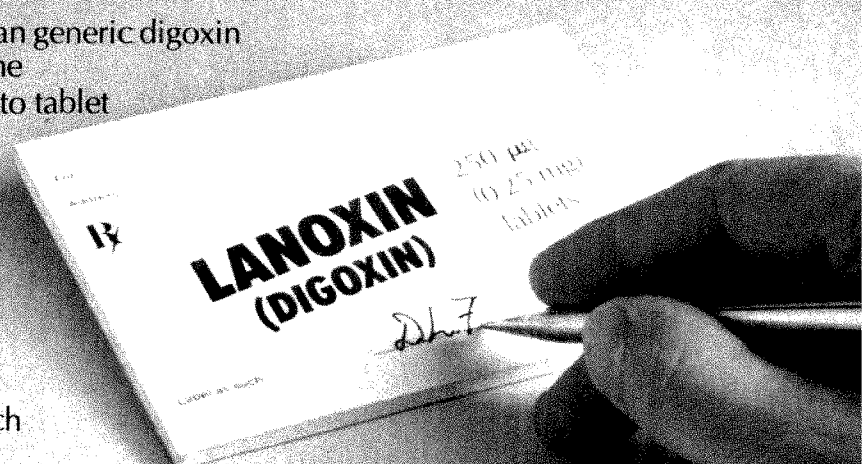

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CLINICAL STUDIES

Medical Versus Surgical Treatment of Unstable Angina

HERBERT N. HULTGREN, MD, UDIPI R. SHETTIGAR, MD, and D. CRAIG MILLER, MD

A prospective, nonrandomized data bank study of the effect of medical versus surgical management of patients with unstable angina included all patients with unstable angina seen at 1 hospital over an 8 year period. Patients were entered into the study after an initial 5 day period of medical treatment. Entry characteristics were similar in 104 surgical patients and 124 medical patients. The mean follow-up period was 52 months. The operative mortality rate was 2% (2 of 104). The incidence of operative infarction was 13% (13 of 104). Twenty-seven medical patients (22%) had late surgery for progressive angina without operative mortality. Seven year survival (Mantel-Haenszel) was 65% for the medical group and 85% for the surgical group when analyzed by initial treatment ($p = 0.012$). Analysis by the crossover method where crossover medical patients are followed up only to the date of surgery yielded similar results ($p = 0.008$). Nonsurvivors were compared with survivors and had a higher incidence of the following entry characteristics: (1) age greater than 60 years; (2) diastolic blood pressure greater than 89 mm Hg; (3) ST-T changes in the resting electrocardiogram; (4) 3 vessel disease; (5) elevated left ventricular diastolic pressure (at rest); and (6) elevated left ventricular diastolic pressure (exercise). None had single vessel disease. The incidence of infarction (fatal and nonfatal) in 5 years was 17% in the medical group and 22% in the surgical group. In the latter group 13% had a perioperative infarct and 9% had a late infarct. Symptom relief was greater in the surgical group. At 5 years 62% had no angina and only 8% had severe angina compared with 37% and 24%, respectively, in the medical group. Thus surgical management of selected patients with unstable angina appears preferable to medical therapy in view of improved survival and greater symptom relief. Whereas the total incidence of infarction was not reduced this was, in part, related to a 13% incidence of perioperative infarction. Improved methods of myocardial protection have since reduced this incidence to 3.0% in our hospital.

Several prospective randomized studies of medical versus surgical management of unstable angina have resulted in the following general conclusions after a 2 to 3 year follow-up period[1-4]: (1) A preliminary period of intensive medical management of 4 to 5 days before surgical treatment is not hazardous and appears to result in a lower operative mortality and morbidity. (2) Surgical treatment provides superior symptomatic relief compared with medical treatment. (3) The incidence of failures in medical treatment over a 3 year follow-up period is appreciable (20 to 39%). Such patients usually exhibit excellent relief of symptoms after coronary bypass surgery. (4) The incidence of perioperative infarction is sufficiently high so that the incidence of infarction is similar in both treatment groups after a follow-up period of 2 to 3 years. (5) Patients without left main coronary artery disease do not exhibit improved survival with surgical therapy compared with those in medical treatment alone. Large scale randomized studies with a longer follow-up period will provide more

From the Cardiology and Cardiovascular Surgery Services, Veterans Administration Medical Center, Palo Alto, California. This study was supported in part by research funds from the Veterans Administration, Palo Alto California. Manuscript received July 6, 1981; revised manuscript received May 3, 1982, accepted May 6, 1982.

Address for reprints: Herbert N. Hultgren, MD, Cardiology Service, Veterans Administration Medical Center, 3801 Miranda Avenue, Palo Alto, California 94304.

secure data regarding the effect of treatment methods on survival and the incidence of nonfatal infarction.

A prospective, randomized study is statistically the most sound approach to the evaluation of 2 modes of therapy. Such studies usually ensure that the 2 treatment groups are identical, and bias in the assignment of patients to treatment groups is avoided. However, the randomized study still presents several problems in the application of data to clinical practice. The patients selected for entry into a randomized study may not be representative of all the patients with the disease entity being studied. Physicians may be unwilling to enter a patient into a study for reasons of personal bias. Physicians may, for example, prefer to treat patients with mild symptoms medically, but in the presence of severe or persisting symptoms surgical treatment may be selected. Patients may be unwilling to enter a study in which their treatment is determined by chance. In published randomized studies of unstable angina it is not known how many eligible patients were not entered.

This problem is avoided in prospective data bank studies in which all eligible patients are entered into the study. If the selection of therapy is largely a random process the 2 treatment groups may have similar entry descriptors and thus a statistically valid comparison of outcome can be attained. If this is not the case patients in predetermined subgroups can be matched regarding important entry descriptors that determine survival.

A preliminary report of the results of therapy in unstable angina in a consecutive series of patients seen at this hospital from 1970 to 1975 has been published.[5] The entry descriptors of the 2 treatment groups were similar. Because the study included all eligible patients seen at 1 hospital and surgery was performed by a single, experienced operating team with a low operative mortality, this study was continued for an additional 2 years. We report herein the results of this investigation up to August 1, 1980.

Methods

Definition of unstable angina: All patients fulfilled at least 1 of the following clinical criteria of unstable angina: (1) stable angina with an increase in severity or frequency of symptoms over the preceding 2 months; (2) recent onset angina with increasing severity or frequency of symptoms over the preceding 2 months (rest angina was not a requirement of these 2 groups); (3) acute coronary insufficiency with at least 1 episode lasting more than 15 minutes within the preceding 2 weeks. Acute coronary insufficiency was defined as prolonged (more than 15 minutes) anginal pain occurring at rest and not promptly relieved by nitrates. Patients with acute myocardial infarction within 3 months of hospital entry were excluded. An additional entry criterion was the presence of transient ST-T wave changes compatible with ischemia. If such changes were not present a positive electrocardiographic exercise test was required.

Acute myocardial infarction excluded patients from the study. The appearance of new Q waves or persistent T-wave inversion associated with significant enzyme elevation was considered evidence of acute infarction.

Daily serum enzyme levels were determined in all patients during the initial hospital study. If 2 successive levels of serum creatine kinase, glutamic oxaloacetic transaminase and lactic dehydrogenase were elevated more than twice the upper limit of normal, the patient was excluded from the study. MB fractions of serum creatine kinase were not obtained in patients who were in the earlier years of the study.

TABLE I Clinical Presentation in 228 Patients With Unstable Angina

	Medical Group (n = 124)	Surgical Group (n = 104)
Stable angina, increased severity (%)	51	72
Angina of recent onset (%)	23	22
Acute coronary insufficiency (%)		
With other symptoms	71	67
Alone	19	12
Mean duration of acute symptoms (days)	17	25
Chest pain >48 h in hospital (%)	34	35

Hospital observation period: A 5 day hospital observation period was a requirement of the study. Patients who died, who had an acute myocardial infarction, or who had complications that would be a contraindication to surgical treatment during the observation period were excluded from the study.

Study group: All patients who were admitted to the hospital from January 1970 to July 1977 who fulfilled the above entry criteria were included in the study. Patients who had any condition that would be a contraindication to coronary bypass surgery were excluded. A total of 124 patients at entry received medical management and 104 patients had surgical treatment.

Coronary arteriography: All patients who had surgical treatment had coronary arteriography and left ventricular angiography. Not all medical patients had arteriography, especially in the earlier years of the study because at that time the risk of arteriography was greater, the importance of left main coronary disease was not appreciated, and arteriography was not considered essential for the initiation of medical treatment. A total of 184 patients had coronary arteriography. This included 104 surgical patients (100%) and 80 medical patients (65%).

Treadmill tests: The Bruce protocol was used in these tests. A test was considered positive when an S-T depression of 0.1 mV or more with a duration of 0.08 or more occurred during or immediately after a symptom-limited test. Treadmill tests were performed in 56 surgical patients (54%) before operation and in 81 medical patients (66%).

Chest roentgenograms were not systematically evaluated in the previous study. In this study chest films were retrieved on all available patients and the cardiothoracic ratio and cardiac volume were calculated by a single observer using standard methods.[6]

Other details of the methods have been summarized in a previous report.[5]

End-points: The following data end-points were used in the evaluation of therapy: (1) *Death* after 5 days of hospital admission or during the follow-up period. (2) *Acute myocardial infarction* after 5 days of hospital admission: Acute infarction was diagnosed when new significant Q waves appeared with evolutionary changes in the presence of a compatible clinical presentation. Perioperative infarction was diagnosed using the same criteria. (3) *Hospital readmission for cardiac reasons:* These reasons included recurrent episodes of angina, acute coronary insufficiency, suspected or proved myocardial infarction, congestive heart failure, cardiac arrhythmia, or postoperative complications. (4) *Relief of*

TABLE II Risk Factors at Entry in 228 Patients With Unstable Angina

	Medical Group (n = 124)	Surgical Group (n = 104)
Age (yr)	58	55
Positive family history (%)	44	40
History of diabetes (%)	13	19
Smoking (%)	81	83
History of hypertension (%)	48	44
Blood pressure (mm Hg)		
Mean systolic (range)	128 (90–220)	126 (100–200)
Mean diastolic (range)	85 (50–130)	85 (50–125)
Systolic >149	29	25
Diastolic >89	34	31
Serum cholesterol (mg/100 ml)		
Mean (range)	250 (101–450)	250 (161–425)
≥250	34	38

BP = blood pressure.

angina: Angina was evaluated as absent, moderate or severe on the basis of the average level of symptoms over 1 month before the follow-up interview. Angina was described as absent when no chest pain had been noted for the preceding month. Moderate angina consisted of episodes that occurred at least weekly but not daily, were easily relieved by nitrates, and did not interfere with normal activity. Anginal episodes that occurred daily and limited normal activity were classified as severe. (5) *Medical treatment failures:* Patients in the medical management group who had subsequent aortocoronary bypass surgery for persisting symptoms despite adequate medical treatment were classified as medical treatment failures (medical crossovers).

Data analysis: Data on each patient were entered in a card file system and analyzed using the Statistical Package for the Social Sciences (SPSS) routine at the Stanford Computation Center. Student's unpaired t tests were used to compare entry data for the patients in the group with unstable angina. Paired t tests were used to assess the statistical significance of changes in variables over the follow-up period in both groups. P values greater than 0.05 were not considered significant. Survival curves were constructed in a standard manner. Comparisons between the 2 treatment groups were made up to 7 years of follow-up by the Mantel-Haenszel test. Survival was evaluated in the following manner: (1) initial treatment assigned; (2) crossover method. Medical patients who had late surgery (Med-ops) were counted as lost to follow-up at the time of surgery. Total deaths and cardiac deaths were analyzed separately.

Exclusions: A total of 238 patients met the initial diagnostic criteria for unstable angina after 48 hours of hospitalization. Ten of these patients were excluded from the study.

TABLE III Electrocardiographic Data in 228 Patients With Unstable Angina

	Medical Group	Surgical Group
Acute changes (%)		
T-wave inversion	60	55
S-T depression	41	43
S-T elevation	21	22
Stable infarct pattern (%)	50	41

TABLE IV Treadmill Test Results in Patients With Unstable Angina

	Medical Group	Surgical Group
Patient (n)	81	56
Positive tests (%)	72	77
Mean duration of exercise (s)	344	346
Mean maximal heart rate (beats/min)	128	133
Mean double product (systolic BP × heart rate ÷ 100)	204	208

Five had an acute nonfatal infarction before the 6th hospital day. Two patients had insufficient coronary disease and 2 had inoperable coronary disease. One patient died on the 3rd hospital day from acute infarction.

Results

Comparability of treatment groups: *Clinical presentation:* The clinical features of unstable angina in the 2 treatment groups are summarized in Table I. These features are similar in the 2 groups except for a larger number of surgical patients who had stable angina with increasing symptoms (72 versus 51%). This difference is not statistically significant.

Risk factors in the 2 groups at entry are summarized in Table II. There are no significant differences.

Electrocardiographic data: The data from the resting electrocardiograms are similar in the 2 groups (Table III). In the medical group slightly more patients had electrocardiographic evidence of prior infarction. This difference is not significant.

Treadmill tests (Table IV): No differences are present.

Chest roentgenograms: The cardiothoracic ratios and the cardiac volumes of the 2 treatment groups are summarized in Table V. There was no significant difference in the prevalence of cardiothoracic ratios greater than 50%.

Increase in serum enzyme level: It is well recognized that many patients with unstable angina may have a modest, transient increase in serum enzyme level. Table VI indicates the mean value of the single highest serum enzyme determination observed during the first 48 hours of hospitalization in the 2 treatment groups. No significant differences are evident.

Hemodynamic features: The arteriovenous oxygen differences and left ventricular end-diastolic pressures are summarized in Table VII. The surgical group had slightly higher left ventricular end-diastolic pressure

TABLE V Chest Roentgenographic Data in Patients With Unstable Angina

	Medical Group	Surgical Group
Patients (n)	69	55
Mean cardiothoracic ratio (%)	44.2	44.6
Cardiothoracic ratio ≥50% (%)	23	25
Mean estimated cardiac volume (ml)	511	510

TABLE VI Highest Serum Enzyme Values* During Hospital Observation Period in 216 Patients With Unstable Angina

	Medical Group	Surgical Group
Patients (n)	118	98
Mean creatine kinase (range)	89 (1–537)	53 (3–481)
Creatine kinase >2 times upper limit of normal (%)	17	9
Mean serum glutamic oxaloacetic transaminase (range)	38 (9–144)	31 (2–151)
Mean lactic dehydrogenase (range)	225 (10–950)	222 (79–1100)

* The upper limits of normal in our hospital are as follows: creatine kinase 75, serum glutamic oxaloacetic transaminase 40, and lactate dehydrogenase 300 units.

both before and after contrast medium injection. These differences are not significant.

Angiographic data (Table VIII): The incidence of left main coronary disease was greater in the surgical group (12.5%) than in the medical group (7.1%). This difference is not significant. The surgical group had a lower incidence of 1 and 2 vessel disease and a higher incidence of 3 vessel disease. These differences are not significant.

Surgical treatment: Aortocoronary bypass surgery was performed in 104 patients initially selected for surgical management. The 30 day operative mortality rate was 2%. Perioperative infarcts occurred in 13 patients (13%). All of these patients had new, persisting Q waves plus diagnostic serum enzyme elevations. Surgery was performed at a later date in 27 medical patients with no operative deaths and 4 perioperative infarctions (14%).

The results of surgery in the initial surgical group of 104 patients are summarized in Table IX. Late shunt angiograms were performed in 37 patients (35%) a mean of 12 months after surgery. Twenty-four patients (66%) had all grafts open and 3 (8%) had all grafts closed. Ninety-two % of patients had at least 1 patent graft.

Follow-up results (Table X): Follow-up data to September 1, 1979 are available on 96 medical patients

TABLE VII Hemodynamic Features of Patients With Unstable Angina

	Medical Group		Surgical Group	
	Patients (n)	Mean Value	Patients (n)	Mean Value
Mean arteriovenous oxygen difference (ml/100 ml)	35	4.7	30	4.6
Left ventricular end-diastolic pressure (mm Hg)				
Pre-LV angiography	53	11.2	62	12.6
Pre-LV angiography >12	14	26	21	34
Post-LV angiography	52	20.0	61	20.9
Post-LV angiography >20	18	34	23	37

LV = left ventricle; LVEDP = left ventricular end-diastolic pressure.

TABLE VIII Angiographic Features of Patients With Unstable Angina

	Medical Group	Surgical Group
Patients (n)	70	104
Number of coronary vessels involved (%)		
1	23	15
2	28	19
3	49	66
Vessels involved (%)		
Left main	7.1	12.5
LAD	74	88
Right	75	81
Left circumflex marginal	74	75
LV contraction (%)		
Normal	36	36
Moderately abnormal	47	45
Severely abnormal	16	18
Mean ejection fraction (%)	68	67
Ejection fraction <50% (%)	15	15

LAD = left anterior descending artery; LV = left ventricular.

(77.4%) and 94 surgical patients (90%). The mean follow-up duration is 52 months, and all patients have been followed up for at least 14 months. Fifty-eight patients have been followed up for 5 years.

In the medical group the overall mortality rate was 18.5%, compared with 10% in the surgical group. The incidence of cardiac deaths in the medical group was 15% compared with 10% in the surgical group. These differences are statistically significant ($p < 0.005$). When patients with left main coronary disease were removed from each group the difference was essentially unchanged. A 2-way analysis of survival at 7 years demonstrated improved survival in the surgical group. The analysis included (1) treatment initially chosen; medical crossovers are counted as patients treated medically; and (2) the crossover method; medical crossovers are counted as lost to follow-up at the time of operation.

In each of the analyses there was a significantly greater improvement in survival in the surgical patients than in the medically treated patients. The results are the same for total mortality and cardiac mortality as end-points (Table XI, Fig. 1 and 2.)

The total incidence of myocardial infarction (fatal and nonfatal) was 17% in the medical group and 22% in the surgical group. The infarcts in the surgical group

TABLE IX Surgical Results in 104 Patients With Unstable Angina

Operations performed (n)	104
Single graft	20
Double graft	49
Triple graft	31
More than 3 grafts	3
Endarterectomy or venous patch grafts	3
Operative mortality (%)	2
Perioperative infarcts (%)	13
Mean interval from hospital admission to surgery (range)	15 (1–120)
Graft patency studies (37 patients)	
All grafts open (%)	66
One or more grafts closed (%)	26
All grafts closed (%)	8

TABLE X Follow-Up Results for Medical Versus Surgical Treatment in Unstable Angina

	Medical Group	Surgical Group	p
Patients (n)	124	104	. . .
Mean follow-up time (mo) (range)	52 (6–96)	52 (6–96)	NS
Total nonfatal infarcts (%)	17	22	NS
Early nonfatal infarcts (<30 days) (%)	7	16	NS
Mortality (%)	18.5	10	0.012
Deaths (n)	23	10	. . .
Angina (%)			
None	37	62	<0.01
Moderate	39	30	NS
Severe	24	8	<0.001
Late hospital entry (%)	32	40	NS
Late operations (%)	22	2	. . .

NS = not significant; p = probability.

TABLE XI Analysis of Survival

	Survival in Medical Group (%)	Survival in Surgical Group (%)	p by M-H at 7 years
Initial treatment (%)			
Total deaths	65	84	0.012
Cardiac deaths	68	87	0.015
Crossover method (%)			
Total deaths	64	84	0.008
Cardiac deaths	68	87	0.015

M-H = Mantel-Haenszel test; p = probability.

TABLE XII Symptoms in Unstable Angina: Comparison of Medical Versus Surgical Treatment*

	Medical Group	Surgical Group
Number	85	118
No angina (%)	27	63
Moderate angina (%)	46	27
Severe angina (%)	27	10
Mean propranolol dose (mg)†	170	112
Used nitroglycerin >10 times a week	19	15

* All surgical patients versus patients who remained on medical treatment.
† Mean value for those patients taking propranolol.

included the 13% incidence of nonfatal perioperative infarcts (Table X, Fig. 3).

The degree of relief of angina was substantially greater in the surgical group. Sixty-three % of the surgical patients had no angina at 39 months compared with 27% of the medical group. Only 10% of the surgical group had severe angina compared with 27% of the medical group.

Further data indicating more substantial relief of angina in the surgical group are shown in Table XII. Sixty-three % of surgical patients were taking no medication for angina and the mean propranolol dose for surgical patients taking propranolol was 112 mg/day. In contrast, only 28% of the medical group was not taking propranolol and the mean propranolol dose for medical patients was 170 mg/day.

The incidence of late hospital entries for cardiac symptoms was similar in both groups. Forty percent of the surgical group had at least 1 late hospital entry, compared to 32% of the medical patients. Hospital entries purely for elective follow-up studies or noncardiac reasons were excluded.

Late surgery in medically treated patients: Twenty-seven patients (22%) who initially received medical treatment had late surgery at a mean interval of 15 months (Fig. 4). No operative deaths occurred in this group, and 1 late cardiac death occurred (4%) over a mean postoperative follow-up period of 32 months. At follow-up 63% were free of angina. The reasons for late surgery were (1) progressive angina, 80%; (2) recurrent unstable angina, 10%; and (3) other reasons, 10%. Entry characteristics were compared for patients who adhered to medical treatment and medical crossovers to surgery. At entry medical patients who crossed over to surgery

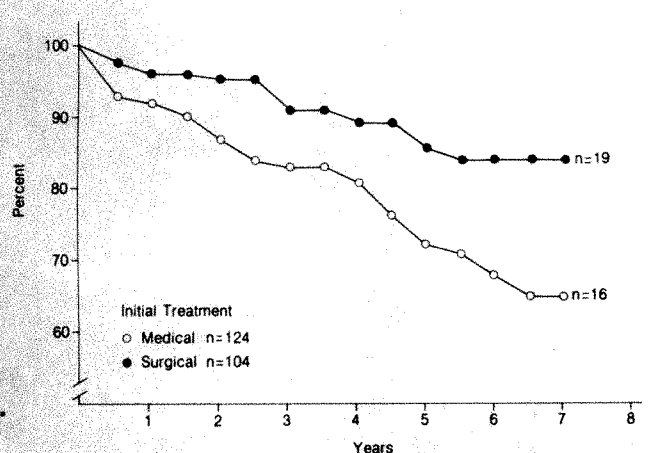

FIGURE 1. Survival curves for patients according to initial treatment. Mantel-Haenszel test at 7 years, p = 0.012.

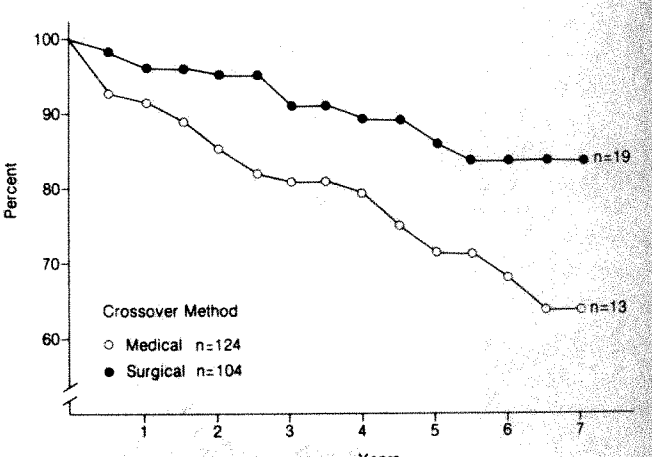

FIGURE 2. Survival curves for patients analyzed by crossover method (medical patients included only to the date of surgery). Total deaths. Mantel-Haenszel test at 7 years, p = 0.008.

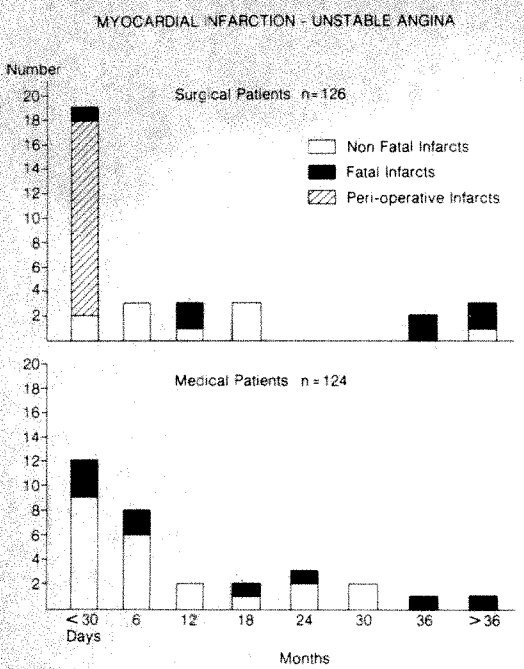

FIGURE 3. Fatal, nonfatal, and perioperative myocardial infarction. Crossovers are included in the surgical group from the date of surgery.

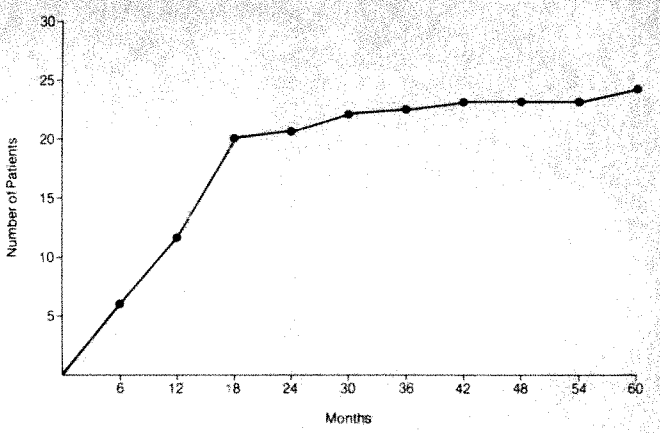

FIGURE 4. Time of surgery in medical crossover patients from the date of entry.

had a higher incidence of the following characteristics than those who adhered to medical therapy: (1) prior myocardial infarction (70 versus 44%); (2) level of serum creatinine kinase elevation during the initial 3 days of hospital observation (121 versus 66 units); (3) shorter duration of treadmill exercise (273 versus 369 seconds); (4) 3 vessel coronary disease (60 versus 43%); and (5) left ventricular contraction abnormalities demonstrated by angiography (72 versus 60%).

Cause and mode of death (Table XIII): Sudden death was more common in the medical group.

Risk factor analysis: Risk factors were evaluated in all patients who died (Table XIV, Fig. 5). The following entry descriptors were more common in patients who died than in survivors: age greater than 60 years, diastolic blood pressure greater than 89 mm Hg, S-T depression, S-T elevation, 3 vessel coronary disease, left main coronary disease, and an elevated left ventricular diastolic pressure at rest and during exercise. No patient who died had single vessel coronary disease.

TABLE XIII Cause and Mode of Death in Patients With Unstable Angina

	Medical Group		Surgical Group	
	n	%*	n	%*
Deaths	23	. . .	10	. . .
Cause				
Operative	0	0	2	20
Myocardial infarction	11	48	5	40
Congestive failure or pulmonary edema	3	13	1	10
Other cardiac	5	22	1	10
Noncardiac	4	17	1	10
Mode				
Sudden†	10	43	2	20

* Percent of all deaths.
† Death within 24 hours of the onset of symptoms outside the hospital.

Discussion

This study shows that surgical treatment of unstable angina is accompanied by a moderate improvement in survival compared with medical treatment. This is apparent even when patients with left main coronary disease are excluded. It is not significantly altered when total deaths are counted compared with cardiac deaths. The influence of medical crossovers does not appear to be responsible for the difference.

Randomized studies of medical versus surgical treatment of stable angina have reported no difference in survival in medically treated patients and patients who had surgery when the total study group was evaluated.[1-4,7-10] If high risk subgroups are defined 3 groups appear to demonstrate improved survival on surgical treatment: (1) patients with left main coronary disease; (2) patients with the following noninvasive risk factors: S-T segment depression in the resting electrocardiogram, history of myocardial infarction, history of hypertension, and New York Heart Association functional class III or IV[10]; and (3) patients with 3 vessel coronary disease and some abnormality of left ventricular function.[9]

Using a data bank-matching method Hammermeister et al.[12] have shown that patients with 2 vessel disease and a reduced ejection fraction also have improved survival with surgical treatment.

Controlled studies of unstable angina have contained an insufficient number of patients to examine survival in subgroups. However, it seems likely that medically treated unstable angina is associated with a higher mortality than medically treated stable angina. The 2 year mortality rate in patients with nonleft main coronary disease with stable angina in the Veterans Administration Cooperative Study medical group was 8%. In the present study the mortality rate was 18.5%. Data

TABLE XIV Risk Factors in Survivors Compared With Nonsurvivors

	Survivors (195)		Nonsurvivors (33)	
	n	%	n	%
Noninvasive factors				
Diastolic BP >90 mm Hg	. . .	31	18	55
S-T depression	73	37	21	64
S-T elevation	29	15	9	27
Invasive factors				
Single vessel disease	32	33	0	0
Triple vessel disease	88	62	. . .	81
LVEDP >12 mm Hg at rest	30	29	. . .	41
LVEDP >12 mm Hg on exercise	33	32	. . .	67

Abbreviations as before.

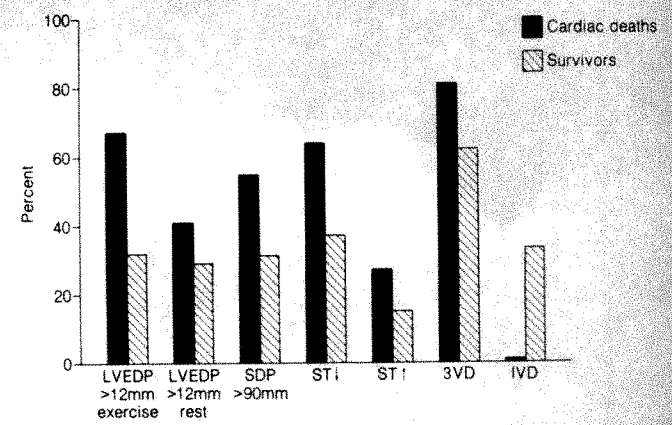

FIGURE 5. Differences between cardiac deaths and survivors. LVEDP = left ventricular end-diastolic pressure; SBP = systolic blood pressure at entry; ST↓ = S-T segment depression on electrocardiography at entry; ST↑ = S-T segment elevation; 3VD = 3 vessel disease; 1VD = 1 vessel disease.

bank studies at Duke University have shown that progressive angina was associated with a higher mortality in patients on medical treatment than in those with stable angina.[12] In Hammermeister's patient group which showed improved survival with surgical therapy in subgroups, 40% had progressive or probable unstable angina. For these reasons an improvement in survival by surgical therapy is not unexpected in patients with unstable angina.

The present study confirms nearly all of the findings of the Cooperative Unstable Angina Study Group (MIRU) except in comparative survival. Comparison of the essential entry features of patients in the MIRU Study and those in the present study reveals very few significant differences.[2,3] This suggests that the MIRU Study group was representative of patients with unstable angina. The difference in survival does not appear to be due to differences in surgical skill because in both studies the operative mortality rate was low and the total morality rate in the surgical group was essentially the same (8 versus 10%). The principal difference was a high mortality in the medical group in the present study (18.5%), versus 9% in the MIRU Study ($p < 0.05$). The high incidence of crossovers and the short follow-up time in the MIRU Study limited the evaluation of comparative survival data.

The present study can be criticized because it was not a prospective randomized study. If randomization had been employed it is very doubtful that a sufficient number of patients would have been entered to achieve any significant data. The acceptability of a data bank approach has been demonstrated by other workers.[12,13] However, these studies have the weakness of being retrospective studies, and the selection of patients is based on the coronary arteriograms. The present study has avoided these problems by being a prospective study with patients selected on the basis of well-defined, objective entry criteria.

A limitation of the study is that only 65% of the medical patients had arteriography. It might be argued that the patients without angiography had more severe disease than those who had angiography, thus introducing a bias in favor of surgical therapy. To examine this possibility the 44 medical patients without angiography were compared with the 80 medical patients who had angiography. Noninvasive entry characteristics including the results of treadmill tests were similar in the 2 groups. The 5 year mortality rate was essentially the same in patients who did not undergo angiography (39%) as in patients who had undergone angiography (43%). The symptomatic status at 5 years was similar in both groups. For these reasons it is unlikely that the patients without angiography had biased the follow-up results.

Three aspects of the management of unstable angina deserve final comments in view of the results of this study:

1. Prevention of myocardial infarction: The low incidence of intrahospital infarction during the initial cooling off period may well be due to the intensive medical therapy with beta-adrenergic blocking agents and nitrates. This therapy is now generally accepted. The incidence of perioperative infarction has been reduced significantly in our hospital over the last 5 years, and the current incidence in patients with unstable angina is 3.0%. Thus with modern methods of myocardial protection the total incidence of infarction in surgically treated patients may become substantially lower than one would expect from medical treatment alone. The mean interval from hospital admission to surgery in the present study was 15 days. The incidence of perioperative infarction may be reduced by a longer waiting period between the onset of unstable angina and surgery. No data are available to support this possibility, but information for large scale studies should be examined with this possibility in mind.

2. Improvement in survival: Although overall survival in unstable angina appears to be improved by surgery as suggested by the present study, high risk subgroups of patients will probably exhibit the most striking improvement in survival. In stable angina such high risk groups can be identified by noninvasive methods.[10] The present study suggests that improved survival will probably be evident in patients over age 60 years who

have diastolic hypertension and ST-T wave changes in the resting electrocardiogram. Invasive features of high risk patients are 3 vessel coronary disease and elevated left ventricular end-diastolic pressure at rest and during exercise (pulmonary arterial wedge pressure). Patients with single vessel disease should be considered surgical candidates only for relief of symptoms.

3. Relief of symptoms and medical treatment failures: Is it possible to predict medical treatment failures from entry characteristics? The present study suggests that the following features were more commonly observed in patients who failed to obtain optimal symptom relief on medical therapy and subsequently had late surgery: prior infarction, poor treadmill performance, serum creatine kinase elevation, 3 vessel disease, and left ventricular contraction abnormalities.

It is hoped that further studies such as the current Veterans Administration Cooperative Study of Unstable Angina will provide an opportunity to examine critically these possibilities.

Addendum

Additional follow-up of all patients up to July 1981 revealed 11 additional deaths in the medical group and 4 additional deaths in the surgical group, indicating a continuing trend toward better survival in the surgical group.

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Characteristics of Survivors of Exertion- and Nonexertion- Related Cardiac Arrest: Value of Subsequent Exercise Testing

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Ninety ambulatory patients previously resuscitated from out-of-hospital ventricular fibrillation underwent treadmill exercise testing an average of 11.5 months after the episode. The level of physical activity immediately before cardiac arrest was known in 86 patients: 23 (27%) had had ventricular fibrillation in association with exertion and 63 (73%) while performing low level activity. Prodromal chest pain and evidence of acute myocardial infarction occurred in a similar proportion of both activity groups. Subsequent exercise test results showed few differences between the groups. Angina occurred in only 11 patients and exercise evoked "ischemic" S-T change in less than half of each group. More of the patients who had collapsed during nonexertional activities had exercise-evoked complex ventricular arrhythmias than did patients who had collapsed during exertion: 33 (52%) versus 6 (26%), respectively ($p < 0.05$).

The 90 patients were followed up for 2 or more years. At 24 months of follow-up, there were 27 deaths of which 19 were due to unexpected cardiac arrest. Only 2 findings on exercise testing were associated with subsequent fatal events. Seven of 11 patients (64%) who had angina during testing had cardiac arrest or died, compared with 20 patients (25%) who had stopped for other reasons ($p < 0.01$). Failure of systolic arterial pressure to rise 10 mm Hg or more during the test was also associated with poor survival: respective mortality at 2 and 4 years was 54 and 69% in those with this abnormal response, compared with 26 and 42% at 2 and 4 years in those whose pressure rose normally ($p < 0.004$).

In the majority of patients ventricular fibrillation developed at low activity levels, and no characteristics were found unique to those who collapsed during exertion. Routine exercise testing was of limited value in the assessment of patients previously resuscitated from cardiac arrest. Exercise-evoked angina and systolic hypotension were highly associated with outcome; however, their ability to predict survival for individual patients was only modest.

In Seattle, approximately 100 victims of out-of-hospital cardiac arrest are resuscitated and ultimately discharged from the hospital each year.[1] Earlier reports showed that most survivors have a history of cardiovascular disease[2] and that about 20% develop evidence of acute transmural myocardial infarction in association with ventricular fibrillation.[3] The majority of survivors have 2 or 3 vessel coronary disease, and many demonstrate marked left ventricular contraction abnormalities, both of which are strongly associated with subsequent episodes of cardiac arrest.[4]

The mechanisms causing ventricular fibrillation are probably multiple. Sudden cardiac arrest may occur during or after vigorous physical exertion; more commonly it is an unexpected event during sedentary activity. In this study, we examined the clinical characteristics of 90 patients with coronary heart disease who had been resuscitated from ventricular fibrillation and who also had subsequent symptom-limited treadmill exercise testing. We compared the clinical findings and

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results of exercise testing in patients who had developed ventricular fibrillation in association with exertion with the group who had collapsed while sedentary or while engaged in minimal physical activity. Through these comparisons we sought to examine relationships among physical exertion, acute myocardial ischemia, and sudden cardiac death.

Methods

Patients: Ninety patients previously resuscitated from ventricular fibrillation by the Seattle Fire Department's emergency care system participated in the study. All had coronary heart disease on the basis of typical clinical or laboratory data, that is, a history of angina or heart attack, electrocardiographic criteria of transmural myocardial infarction, or coronary angiography. Patients with other heart diseases were excluded from this study, as were a small number with no evident heart disease. Coronary angiography was performed in 35 (39%) of the patients at the discretion of the patient's personal physicians.

Level of physical activity before cardiac arrest: The level of physical activity immediately before collapse and cardiac arrest could be determined in 86 patients through interviews with the patient or witnesses to the episode of cardiac arrest. Interviews were done shortly after the arrest, usually within 1 month. Activities were categorized as (1) sedentary, (2) ambulatory, or (3) exertional. Exertion included: participation in active sports, vigorous exercise, dancing, or heavy manual work. Ambulatory activities included walking, standing, or personal hygiene. Bed rest and sitting were classified as sedentary activities. This activity level at the time of cardiac arrest was used to determine an arrest related to exertion and to nonexertion (sedentary or low level activity). Activity level was not determined by overall evaluation of physical training of the victims.

Clinical evaluation and exercise testing: All patients volunteered to participate in a special research clinic after hospital discharge. About 70% of patients resuscitated from out-of-hospital cardiac arrest attend this clinic. It is not possible to be certain whether patients in this report were representative of all victims resuscitated. They may be more motivated or inquisitive and less physically disabled than those who chose not to participate.

A physician interviewed the patient, performed a physical examination, and reviewed the postresuscitation hospital record at the first clinic visit. Disability was assessed at that time using New York Heart Association criteria.[5] If there were no clinical contraindications and if the patient and his personal physician agreed, a multistaged treadmill test was done.[6] Elapsed time from cardiac arrest to exercise testing averaged 11.5 (±12.5 standard deviation) months. Fifty-eight (64%) were tested within 1 year of the event. Results of those tested within 1 year and later were also compared to unmask any possible bias toward outcome.

The duration of treadmill exercise was determined by the patient, who was instructed to stop when limiting symptoms of fatigue, chest pain, shortness of breath, or lightheadedness occurred. Blood pressure was measured by standard cuff technique during the midportion of each exercise level. Cardiac rhythm, heart rate, and S-T segment response were monitored continuously by the oscilloscope and recorded each minute. A single modified V_5 electrode was used.[7] Unsteady gait, fall in systolic blood pressure, increasing ventricular arrhythmia, or evoked complex ventricular arrhythmias were additional indications to stop the test. During the postexercise recovery period, the blood pressure, rhythm, and S-T response were recorded at least every minute for 5 minutes, or until exercise-induced symptoms or electrocardiographic abnormalities resolved. In 23 patients the S-T segment was depressed during the resting tracing in association with digoxin or conduction abnormalities. Accordingly, this group was excluded from further exercise S-T analysis.

Clinical characteristics and exercise test responses were compared in 2 groups of patients: (1) those in whom ventricular fibrillation occurred in association with exertion, and (2) those who developed cardiac arrest while performing sedentary or low levels of activity. Differences in discrete variables were analyzed by the chi-square test and in continuous variables by Student's *t* test. We looked for possible interrelationships between activity group, outcome, time from arrest until exercise testing, and exercise test results using analysis of variance. Survival analyses were done using the product limited method.[8]

Follow-up: All ninety patients were followed up at least 2 years; the average follow-up was 4 years. By 2 years of follow-up, 19 patients (21%) had had unexpected fatal cardiac arrest (n = 15) or were resuscitated from another episode of out-of-hospital ventricular fibrillation (n = 4). Eight others had nonsudden death, usually occurring during a subsequent hospitalization for myocardial infarction or heart failure. Thus, there were 27 fatal events at 2 years. The findings of exercise testing in survivors were compared with the findings in those who died or developed cardiac arrest.

TABLE I Cardiovascular History of 86 Patients With Coronary Heart Disease (CHD) Resuscitated From Out-of-Hospital Ventricular Fibrillation (VF)

	Patients 23 ExVF		Patients 63 Non-ExVF		
	n	%	n	%	p*
History before VF†					
Angina	8	36	28	45	NS
Previous MI	7	32	23	37	NS
Heart failure	2	9	12	19	NS
Any CHD‡	13	57	49	79	<0.05
History before ETT and after VF					
Angina	10	43	26	41	NS
Heart failure	6	26	27	43	NS
Acute necrosis with VF§	7	30	23	37	NS
Functional class‖					
1,2	19	83	37	59	...
3,4	4	17	26	41	<0.05

* Probability (p) values >0.1 between the 2 patient groups are expressed as not significant (NS).
† Clinical history was unknown in 1 case.
‡ Histories of angina, heart failure, and previous infarction are considered together.
§ Presence of new electrocardiographic Q waves or lactic dehydrogenase isoenzyme evidence of myocardial necrosis during the post-VF hospitalization. Enzymes were determined in 74% of ExVF patients and 67% of non-ExVF patients.
‖ New York Heart Association classification.
ETT = exercise tolerance test; ExVF = patients who developed ventricular fibrillation in association with exertion; MI = myocardial infarction; non-ExVF = patients who developed ventricular fibrillation in association with sedentary or mild physical activity.

Results

Patient characteristics (Table I): Of the 86 patients whose physical activity was known immediately before cardiac arrest, 23 (27%) had ventricular fibrillation in association with physical exertion, and 63 pa-

TABLE II Symptoms and Functional Characteristics of Patients During Exercise Testing

	23 ExVF Patients		63 non-ExVF Patients		86 Total Patients	
	n	%	n	%	n	%
Primary limiting reason for terminating test						
Angina	0	0	7	11	7	8
Fatigue	19	83	44	70	63	73
Lightheadedness	0	0	1	2	1	1
Ventricular arrhythmia	4	17	5	8	9	10
Physician limited	0	0	6	10	6	7
Any limitations noted at test termination						
Angina	2	9	9	14	11	13
Fatigue	19	83	44	70	63	86
Lightheadedness	0	0	2	3	2	2
Ventricular arrhythmia	9	39	21	33	30	35
Physician limited	5	22	11	17	16	19
Exercise function						
Treadmill exercise duration (min ± SE)	5.6 ± 0.6*		4.4 ± 0.3*		4.7 ± 0.3	
Average peak heart rate (bpm ± SE)	142.3 ± 3.8		134.1 ± 3.5		136.3 ± 2.7	
Average increase in heart rate (bpm ± SE)	61.9 ± 4.3		60.3 ± 3.1		60.7 ± 2.5	
Average peak BP (mm Hg ± SE)	167.4 ± 6.5		159.2 ± 3.6		161.4 ± 3.2	
Average rise of systolic BP (mm Hg ± SE)	34.3 ± 4.5		25.7 ± 3.1		28.0 ± 2.6	

* Patients with ExVF tended to exercise longer ($p < 0.1$) than did non-ExVF patients.

BP = blood pressure; bpm = beats/min; ExVF = patients who developed ventricular fibrillation in association with exertion; non-ExVF = patients who developed ventricular fibrillation while sedentary or doing low level physical activities; SE = standard error.

TABLE III Cardiac Rhythm and S-T Segment Changes During or After Exercise Testing

	23 ExVF Patients		63 Non-ExVF Patients		86 Total Patients	
	n	%	n	%	n	%
Ventricular arrhythmias						
None	10	43	21	33	31	36
Uniform VPB only	7	30	9	14	16	19
Complex VPB	6	26*	33	52*	39	45
Bigeminy/trigeminy	2	9	18	29	20	23
Multiform VPB	4	17	22	35	26	30
Repetitive VPB	5	22	15	24	20	23
S-T depression of 1 mm or greater†	8	42	20	45	28	44

* Exercise-evoked complex ventricular arrhythmias occurred more often in non-ExVF patients than in ExVF patients ($p < 0.05$).

† In 4 ExVF patients and 19 non-ExVF patients, S-T segment was abnormal at rest; S-T responses in these patients were excluded in the comparison.

ExVF = patients who developed ventricular fibrillation in association with physical exertion; non-ExVF = patients who developed ventricular fibrillation while sedentary or doing low level physical activities; VPB = ventricular premature beats.

tients (73%) had cardiac arrest while sedentary or during low level physical activity. The average ages of the 2 groups were 59.5 and 60.9 years, respectively. All patients in the exertion group were men, whereas 10 of 63 patients in the nonexertion group were women. During the postresuscitation hospitalization, electrocardiographic (new Q waves) or lactic dehydrogenase isoenzyme evidence of acute myocardial necrosis (LDH_1 increased and greater than LDH_2) developed in about one third of all patients; these findings were present in 7 patients in the exertion group (30%) and in 23 of the nonexertion patients (37%). Immediately before cardiac arrest, chest pain was present in 4 patients (27%) who had had ventricular fibrillation during exertion and in 18 (29%) of the nonexertion group. Of the 22 patients who had chest pain preceding cardiac arrest, acute myocardial infarction developed in all 4 of those who collapsed with exertion and in 8 of 18 in the nonexertion group.

The prevalence of individual cardiovascular characteristics (history of either angina, remote myocardial infarction, hypertension, or congestive heart failure) was similar for both patient groups. However, if the histories were considered conjointly, fewer of the patients who had ventricular fibrillation in association with exertion had prior manifestations of cardiovascular disease, compared with those in the nonexertion group (57 versus 79 percent, $p < 0.05$).

The clinical history before cardiac arrest suggested that patients who collapsed during exertion also had less physical disability than did those who collapsed while sedentary. Moderate to severe physical impairment (functional class 3 or 4) was present in 4 patients (17%) in the exertion group compared with 26 (41%) in the nonexertion group ($p < 0.05$).

Exercise test results (Tables II and III): Patients who had developed ventricular fibrillation during exertion tended to exercise longer than did patients in the nonexertion group: 5.6 ± 0.6 (mean ± standard error of the mean) minutes compared with 4.4 ± 0.3 minutes ($p < 0.1$). The reasons for stopping the test were similar in both groups. Angina was induced infrequently; it was the primary reason for terminating the exercise test in only 7 patients (8%) and occurred as a secondary reason in 4 others. Two patients (9%) in the exertion group developed chest pain during the exercise test; neither had had chest pain immediately before cardiac arrest. Leg or generalized fatigue was the usual reason for stopping in nearly three fourths of patients. The attending physician interrupted the test in 10% of patients because of either increasing or complex ventricular arrhythmia. In an additional 21 patients (25%), ventricular arrhythmia was listed as a secondary reason for stopping. In 6 other instances, the test was also terminated by the physician because of concern about the patient's poor physical performance or a fall in blood pressure during exercise testing (Table II). Thus, 36 patients (40%) developed either electrocardiographic or hemodynamic findings that prompted discontinuation of the test.

There were no significant differences between the 2 activity groups in the mean peak heart rate or systolic blood pressure attained during exercise testing. However, more of the exertion group (91%) reached a

peak rate of 130 beats/min or greater than did the patients who had previously collapsed while sedentary (38%). Systolic blood pressure also tended to increase more in the patients with previous exertion-related cardiac arrest.

Ventricular arrhythmias were observed in 64% of patients during exercise or recovery. We did not determine possible serum antiarrhythmic drug levels, and no attempt was made to control for the use of these drugs, which were being taken by half of the patients. Exercise-evoked complex ventricular arrhythmia (bigeminy/trigeminy, multiform beats, or repetitive beats) occurred in a greater proportion of the patients who had collapsed while sedentary than of those who collapsed during exertion: in 33 (52%) versus 6 (26%), respectively ($p < 0.05$). Seven episodes of paroxysmal self-limited ventricular tachycardia occurred (4 or more repetitive beats), all in the nonexertion group.

An "ischemic" S-T segment response (1 mm or more of flat or downsloping depression) developed during or after exercise testing in 28 of 63 tests (44%) in which interpretation was possible. There was no difference in the proportion of the 2 activity groups who developed "ischemic" S-T responses. In addition, we examined the activity groups and exercise test results in patients who were tested within 6 months, 1 year, and more than 1 year after cardiac arrest. The duration from arrest until testing had no significant effect on any of the findings.

Exercise testing and subsequent outcome (Table IV): The overall mortality rates at 1, 2, and 4 years were 20, 30, and 46 percent, respectively. By 2 years after the exercise test, there were 19 unexpected cardiac arrests and 8 additional nonsudden deaths. Survival was similar in the exertion- and nonexertion-related groups. Eight of the patients in the exertion-related group and 15 of those in the nonexertion-related group died. Also, outcome in these 2 groups of patients was not related to the time from cardiac arrest until exercise testing.

Neither the change in heart rate, peak heart rate, and duration of treadmill exercise, nor evoked S-T depression or arrhythmias was related to subsequent sudden or nonsudden death, irrespective of the time from previous arrest to testing. Only 2 observations during the index exercise test were associated with subsequent fatal events: angina and exertional hypotension. Although angina was evoked in only 11 patients, 7 (64%) had a fatal event by the end of 2 years. In contrast, 20 of 79 patients (25%) who stopped the test for other reasons had a recurrent cardiac arrest or nonsudden death ($p < 0.01$) (Fig. 1). Exercise limitations other than chest pain were not related to outcome.

Failure of the systolic blood pressure to increase to 10 mm Hg or more during treadmill exercise was observed in 13 patients and was also associated with poor survival (Fig. 2). The survival rates over the first 4 years were 82, 74, 68, and 58%, respectively, in patients whose blood pressure rose normally compared with 62, 46, 38, and 31% in those whose blood pressure failed to rise ($p = 0.004$). This relationship was valid whether the test

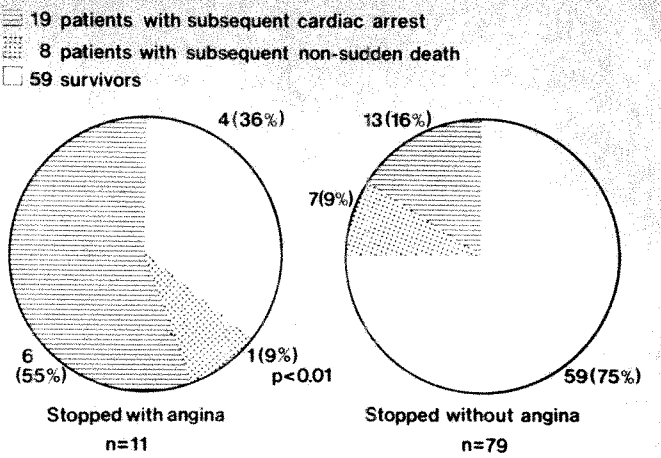

FIGURE 1. Mortality at 2 years of follow-up was greater if angina had occurred during exercise testing. Sixty-four % of those who had angina during testing (**left**) had a subsequent fatal event, compared with 25% of those who had stopped the test for other reasons (**right**) ($p < 0.01$).

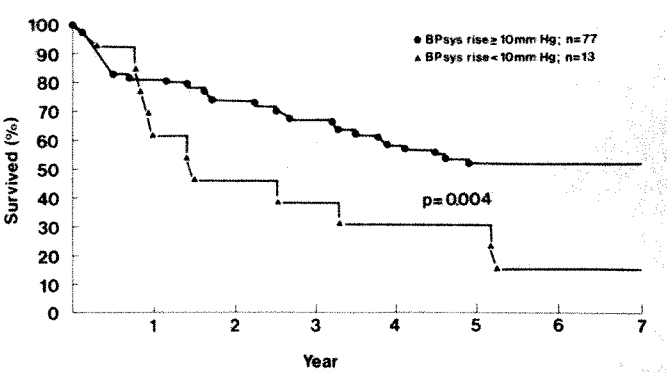

FIGURE 2. Failure to augment systolic blood pressure (BP sys) by 10 mm Hg or more during exercise was associated with significantly worse survival. There were more subsequent sudden and nonsudden deaths in patients whose blood pressure failed to increase normally. Seventy-four % of patients who had a normal response were alive at 2 years, compared with 46% of those in whom exertional hypotension had developed.

had been done within 6 months, 1 year, or longer from the initial event and was unrelated to any of the other observations made during exercise. Only 1 patient exhibited both angina and an impaired augmentation of systolic pressure during the test. By 2 years, 14 of 23 patients (61%) with either of these findings had died, compared with 13 deaths in the 67 patients (19%) not having these findings. At 4 years of follow-up 20 (87%) of this abnormal test group had died, compared with 43% of patients without either of these exercise-evoked findings ($p < 0.0001$).

Despite the strong association between subsequent mortality and exercise-evokd angina or abnormal blood pressure response, the value of these findings as predictors of subsequent cardiac arrest and death was

TABLE IV Exercise Test Results and Subsequent Outcome

	63 Survivors		19 SD/VF		27 Total Deaths*	
	n	%	n	%	n	%
Exercise symptoms						
All limitations						
Angina	4	5	6	32†	7	26†
Fatigue	47	75	14	74	20	74
Arrhythmia	18	29	10	53	12	44
Heart rate (bpm)						
Resting ≥75	33	52	14	74	20	74
Peak						
≥120	52	83	16	84	21	78
≥130	45	71	14	74	17	63
≥140	32	51	10	53	12	44
Exercise ECG findings						
Arrhythmias						
None	24	38	7	37	11	41
Uniform VPB only	12	19	3	16	4	15
Any complex VPB‡	27	40	9	47	12	41
1 mm or greater S-T depression	20/48	42	7/15	47	8/19	42
Exercise function						
Exercise duration (min ± SE)	4.9 ± 0.3		4.7 ± 0.6		4.3 ± 0.5	
Average peak heart rate (bpm ± SE)	137.7 ± 3.4		136.6 ± 4.2		132.9 ± 4.4	
Average increase in heart rate (bpm ± SE)	62.7 ± 3.2		57.5 ± 3.7		54.8 ± 3.8	
Average peak BP (mm Hg ± SE)	164.6 ± 3.8		153.5 ± 6.9		155.0 ± 5.1	
Average rise in BP (mm Hg ± SE)	30.2 ± 2.9		28.7 ± 6.1		23.7 ± 4.9	

* Total deaths (fatal events) include 8 nonsudden events, 15 sudden deaths, and 4 patients who were successfully resuscitated from a subsequent episode of ventricular fibrillation.

† Probability of difference between survivors and SD/VF or survivors versus total deaths, when $p < 0.01$.

‡ Complex VPB = bigeminy/trigeminy; multiform or repetitive VPB.

BP = blood pressure; bpm = beats/min; ECG = electrocardiographic; SD/VF = subsequent sudden death or resuscitation from an episode of ventricular fibrillation; SE = standard error; VPB = ventricular premature beats.

limited. The sensitivity, specificity, and predictive accuracy of evoked angina were 26, 94, and 64%, respectively; and for abnormal systolic pressure increase they were 25, 90, and 54%, respectively.

Discussion

Exertional versus nonexertional cardiac arrest: Twenty-seven percent of our 90 patients, all previously resuscitated from out-of-hospital cardiac arrest, had ventricular fibrillation in association with physical exertion. A similar incidence of exertion-related cardiovascular collapse was reported in another group of resuscitated victims[9] and by registries[10,11] which examined the circumstances associated with instantaneous out-of-hospital death. We had anticipated differences in the clinical characteristics of patients who developed cardiac arrest in association with exertion compared with those who collapsed at low activity levels. However, there were few such differences: symptoms of chest pain just before cardiac arrest, evidence of acute infarction, and development of angina or ischemic S-T responses during subsequent treadmill testing were present in similar proportions of both groups. Clearly, cardiac arrest develops in some patients during or after exertion. During supervised exercise in a Seattle area cardiac rehabilitation program, 23 patients collapsed with cardiac arrest; all had ventricular fibrillation and all were resuscitated.[12,13] Our observations suggest that exertion-related ventricular fibillation is not usually the result of acute infarction. There was also no evidence during subsequent exercise testing of more exertion-evoked ischemia or arrhythmias in patients who had previously collapsed during exertion than in those who had collapsed while sedentary.

Angina and decrease in systolic pressure during exercise testing as predictors of survival: Only 2 findings during exercise testing were associated with a subsequent fatal event. Both sudden and nonsudden death occurred more frequently in patients who had angina during the exercise test, compared with those who stopped the test for other reasons. Also, failure of systolic blood pressure to increase 10 mm Hg or more during stress testing was an unfavorable prognostic sign. "Exertional hypotension" thus may not only portend ventricular fibrillation *during* exercise testing and serve as an indication for stopping the test,[14] but also is prognostic of a subsequent fatal event. Both findings, however, were only modest predictors of outcome. Fourteen of 27 patients who had died by 2 years had either exercise-evoked angina or hypotension (sensitivity 52%, specificity 86%, predictive accuracy 61%).

As our purpose was to examine possible mechanisms of cardiac arrest in activity groups using a noninvasive test and also to use standard exercise testing as a predictor of outcome, we did not regularly perform angiography as a part of this study. We suspect that exertional hypotension and angina occurring in these patients probably results from either severely impaired ventricular function due to previous infarction or to ischemia associated with severe 3 vessel coronary disease. It seems likely that resuscitated patients who develop angina or hypotension during the subsequent exercise testing have these angiographic findings, both of which are associated with subsequent cardiac arrest.[4] It is our present recommendation that cardiac catheterization be performed and coronary bypass surgery considered in suitable candidates who show these exercise abnormalities after resuscitation.

Prognostic role of exercise-induced ventricular arrhythmia: Ventricular arrhythmias evoked during or after exercise were not predictive of subsequent mortality. Complex ventricular arrhythmias occurred in slightly less than half of both survivors and nonsurvivors. This incidence of exercise-induced arrhythmia is similar to other observations during exercise testing of patients with recurrent paroxysmal ventricular tachycardia,[15] but somewhat greater than that found in patients in general with known coronary heart dis-

ease.[16–20] Others[21–23] have suggested that exercise-evoked ventricular arrhythmias in the setting of ischemic heart disease is associated with subsequent sudden death. There are several possible reasons for the apparent discrepancy between those reports and our own. First, our observations concern a select group of patients: all have had a previous episode of out-of-hospital ventricular fibrillation. Second, both of our subsequent outcome groups had a high incidence of exercise-evoked complex arrhythmias compared with that in other studies of patients with coronary heart disease. Additionally, we did not discontinue antiarrhythmic treatment before testing. This may have favorably affected the rhythm, although a similar proportion of both survivors and nonsurvivors were taking these drugs. Although the other reports did demonstrate a statistical association between outcome and exertional arrhythmias, the predictive accuracy was poor and the finding was of limited value in estimating prognosis for a given patient. In view of our findings reported here and those mentioned earlier, we do not feel that exercise-evoked arrhythmias have major prognostic importance in individual tests; that is, they are neither a highly sensitive nor specific predictor of sudden cardiac death. At present we employ electrophysiologic testing to select antiarrhythmic therapy in appropriate patients regardless of the results of exercise testing.

Implications: Contrary to what might be expected, we found no evidence from exercise testing that patients who had previously had ventricular fibrillation in association with exertion had a greater incidence of either evoked ischemia or ventricular arrhythmia than that observed in patients who had collapsed at low levels of physical activity. The mechanism of exertion-related ventricular fibrillation is still unclear. Exercise-evoked angina and S-T evidence of ischemia were surprisingly unusual during testing of patients previously resuscitated from cardiac arrest, and exercise ventricular arrhythmias were not of prognostic import. Routine exercise testing of these patients is of limited use in predicting the outcome for individual patients. However, exercise-evoked angina and systolic hypotension were highly associated with the occurrence of subsequent fatal events.

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Quantitative Comparison of Extent of Coronary Narrowing and Size of Healed Myocardial Infarct in 33 Necropsy Patients With Clinically Recognized and in 28 With Clinically Unrecognized ("Silent") Previous Acute Myocardial Infarction

HENRY SCOTT CABIN, MD and WILLIAM C. ROBERTS, MD

Clinical and necropsy observations are described in 61 patients with a healed transmural myocardial infarction, 33 with and 28 without a clinical history of acute myocardial infarction. There were no significant differences between the 2 groups of patients in mean age, sex, or frequency of angina pectoris, chronic congestive heart failure, systemic hypertension, sudden coronary death, or fatal acute myocardial infarction. Compared with the patients with clinically recognized acute myocardial infarction, the patients with clinically unrecognized (silent) infarction had a significantly ($p < 0.05$) higher incidence of diabetes mellitus (43 versus 15%), death from noncardiac causes (39 versus 9%), posterior (inferior) wall infarcts (82 versus 55%), and smaller infarcts (mean size 7 versus 17% of left ventricular wall). The patients with and without clinically recognized infarction had similar numbers of the 4 major coronary arteries severely (76 to 100% in cross-sectional area) narrowed (mean 2.8 versus 2.9/4.0 per patient), insignificant differences in incidence of severe narrowing of the left main coronary artery (18 versus 29%), similar overall percents of 5 mm segments of the 4 major coronary arteries severely narrowed (43 versus 42%), and similar percents of severely narrowed 5 mm segments of the right (46 versus 55%), left anterior descending (39 versus 33%), and left circumflex (41 versus 41%) coronary arteries.

Some patients with acute myocardial infarction have symptoms and signs indicative of coagulation necrosis of a portion of the left ventricular myocardial wall, and others apparently have no clinical manifestations caused by the myocardial necrosis, that is, the event is clinically silent. Indeed, possibly as many as 50% of acute myocardial infarcts are not recognized clinically.[1-11] Although several previous studies[1-11] have focused on clinically unrecognized acute myocardial infarction, none have compared at necropsy the degrees of coronary arterial narrowing and the extent of the myocardial damage in patients with clinically *recognized* versus those with clinically *unrecognized* acute myocardial infarction that healed. The present study compares the amount of coronary arterial narrowing and left ventricular myocardial scarring in 33 patients with a clinically unrecognized with that in 28 patients with a clinically recognized transmural acute myocardial infarct that healed.

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Methods

Study patients: All 61 study patients had a healed transmural myocardial infarct defined as a left ventricular scar involving more than the inner one half of the thickness of the left ventricular wall at any point.[12] For each patient the medical records were reviewed in detail by at least one of us and the patients were divided into 2 groups according to the presence (33 patients) or absence (28 patients) of a clinical history of acute myocardial infarction. Patients were included in the clinically recognized myocardial infarction group (hereafter referred to as the recognized infarct group) if there was a record of hospitalization for acute myocardial infarction with subsequent confirmation of the diagnosis by established electrocardiographic and enzymatic criteria. All 33 patients

TABLE I Clinical Findings in 33 Patients With Clinically Recognized and in 28 With Clinically Unrecognized Acute Myocardial Infarction (MI) and Healed Transmural Infarction at Necropsy

	Clinically Recognized Acute MI (33 Patients)		Clinically Unrecognized Acute MI (28 Patients)		p Value
	n	%	n	%	
Age (yr)					
Mean	61	...	60	...	NS
Range	27–81	...	25–82	...	
Male:female ratio	25:8	...	21:7	...	NS
Angina pectoris	14	42	6	21	NS
Chronic congestive heart failure	14	42	9	32	NS
Systemic hypertension	11	33	12	43	NS
Diabetes mellitus (adult onset)	5	15	12	43	<0.05
Mode of death					
Sudden	13	39	6	21	NS
Acute MI	8	24	7	25	NS
Chronic congestive heart failure	5	15	1	4	NS
Cardiac operation	2*	6	2†	7	NS
Cardiac catheterization	2	6	1	4	NS
Noncardiac	3	9	11	39	<0.01

* Coronary artery bypass grafting in 1 and left ventricular aneurysmectomy in 1.
† Coronary artery bypass grafting in both.

TABLE II Myocardial Infarct (MI) Size and Location in 33 Patients With and in 28 Without a Clinical History of Acute MI and a Healed Transmural MI at Necropsy

Clinical History of Acute MI	Patients (n)	MI Size (%)		Number of Patients With Major (Minor)* Involvement of Each Left Ventricular Wall by MI			
		Range	Mean	Anterior	Posterior	Septal	Lateral
+	33	1–55	17	16 (1)	15 (3)	1 (12)	1 (14)
0	28	1–23	7	5 (1)	22 (1)	1 (8)	0 (9)
p value	...	<0.001		<0.01	<0.025	NS	NS

* For each patient, major involvement refers to the left ventricular wall with the most scarring and minor involvement refers to 1 or more additional walls with scarring. In all but 3 patients the anterior or posterior wall of left ventricle was the site of major involvement.

TABLE III Number of Major Epicardial Coronary Arteries (CA) Narrowed 76 to 100% in Cross-Sectional Area (XSA) by Atherosclerotic Plaque in 33 Patients With and 28 Without a History of Acute Myocardial Infarction (MI) and a Healed Transmural MI at Necropsy

Clinical History Acute MI	Patients (n)	Total CA (n)	Patients With CA Narrowed 76–100% in XSA										Mean CA per Patient Narrowed 76–100%
			LM		LAD		LC		R		Totals		
			n	%	n	%	n	%	n	%	n	%	
+	33	132	6	18	32	97	23	70	32	97	93	70	2.8
0	28	112	8	29	24	86	21	75	28	100	81	72	2.9
p value	...	...	NS		NS		NS		NS		NS		NS

LAD = left anterior descending; LC = left circumflex; LM = left main; R = right.

had prolonged chest pain at rest. Patients were included in the clinically unrecognized acute myocardial infarction group (hereafter referred to as the unrecognized infarct group) if detailed medical records were available and there was no report of hospitalization for acute myocardial infarction or record of unstable angina pectoris, prolonged chest pain at rest, acute worsening of congestive heart failure or syncope (except within the final 2 months of life). In the patients with unrecognized acute myocardial infarction, electrocardiograms never indicated a pattern consistent with acute myocardial infarction except in the 7 (of 28) patients in whom this event was fatal; all 28 patients, of course, had transmural left ventricular scars. Patients with an equivocal or inadequate history were excluded as were patients with symptoms suggestive of acute myocardial infarction who did not seek hospitalization or who were hospitalized but did not have laboratory confirmation of the diagnosis of acute infarction.

Pathologic examination: In each patient, the heart was cut into 5 or 6 one cm thick transverse ventricular slices from apex to base parallel to the posterior atrioventricular sulcus. The major location of the infarct was determined by identifying the portion of left ventricular wall with the greatest amount of scar. When the infarct was circumferential at the apex, the basal portion of the heart was used to determine the predominant location of the infarct. In all but 3 of the 61 patients the infarct was located predominantly in the anterior

or posterior wall with or without involvement of the ventricular septum or lateral wall (defined as that portion of left ventricular wall between the lateral borders of the anterolateral and posteromedial papillary muscles).

The percent of myocardium replaced by scar was determined by tracing the grossly visible areas of scar and the total left ventricular area including ventricular septum (with compensation for wall thinning in areas of scar) from photographs of the apical surfaces of each transverse ventricular slice. The area of scar and the total left ventricular area were then determined by a videoplanimetry system. The sum of the areas of scarring divided by the sum of the left ventricular areas provided the infarct size expressed as a percent of total left ventricular area.

In each of the 61 patients, the entire lengths of the right, left main, left anterior descending, and left circumflex coronary arteries were removed from the heart intact, fixed in an unpressurized state in 10% formalin for about 48 hours, radiographed, and if calcific deposits were present, decalcified. Then each of the 4 major arteries was cut transversely into 5 mm long segments, processed in alcohol and xylene and cut. At least one 6 μm thick section from each 5 mm segment was prepared for histologic study and stained by the Movat method.[13] The degree of luminal narrowing in each 5 mm long segment was determined by microscopic examination at a magnification of 25 to 50 times. The percent of cross-sectional area narrowing by atherosclerotic plaque was divided into 5 categories of narrowing: 0 to 25, 26 to 50, 51 to 75, 76 to 95, and 96 to 100. The accuracy of these determinations was verified by videoplanimetry and shown to have an error of less than 5 percent.[14]

Statistical analysis: The unpaired and paired Student's *t* test was employed for the quantitative comparisons of coronary narrowing. Chi-square analysis was utilized for comparison of clinical variables and for comparison of amounts of coronary narrowing by qualitative means.

Results

Clinical findings (Table I): Angina pectoris occurred in 14 (42%) of the 33 patients in the recognized infarct group (after the infarct in each) and in 6 (21%) of the 28 patients in the unrecognized infarct group ($p < 0.10$). Diabetes mellitus of adult onset occurred more frequently in the unrecognized than in the recognized infarct group (12 [43%] versus 5 [15%]) ($p < 0.05$). Among the 17 patients with diabetes mellitus, angina pectoris was present in 4 of the 12 patients with clinically unrecognized infarcts and in 2 of the 5 patients with recognized infarcts. Death from noncardiac causes occurred more often in the unrecognized infarct group (11 [39%] versus 3 [9%]) ($p < 0.01$).

Location and size of infarct (Table II): The predominant location of the healed myocardial infarct was the anterior wall of the left ventricle in 16 (48%) of 33 patients from the recognized infarct group and in 5 (18%) of 28 from the unrecognized infarct group ($p < 0.01$); posterior wall in 15 (45%) and 22 (79%), respectively ($p < 0.025$); lateral wall in 1 (3%) and none, respectively (p = NS); and ventriculum septum in 1 (3%) and 1 (4%), respectively (p = NS). The percent of left ventricular myocardium (including ventricular septum) infarcted ranged from 1 to 55 (mean 17) in the recognized infarct group and from 1 to 23 (mean 7) in the unrecognized infarct group ($p < 0.001$).

TABLE IV Number of 33 Patients With and 28 Without a Clinical History of Acute Myocardial Infarction (MI) and a Healed Transmural MI at Necropsy with 0 to 4 of 4 Major Coronary Arteries (CA) Narrowed 76 to 100% in Cross-Sectional Area (XSA) by Atherosclerotic Plaque

CA (n) Narrowed 76–100% in XSA	Clinical History of Acute MI				p Value
	+		0		
	n	%	n	%	
4	5	15	5	18	NS
3	20	61	17	61	NS
2	7	21	4	14	NS
1	1	3	2	7	NS
0	0	...	0	...	NS
Totals	33	100	28	100	...

Incidence of severe coronary narrowing (Tables III and IV): Of the 132 major (right, left main, left anterior descending, and left circumflex) epicardial coronary arteries examined in the 33 patients in the recognized infarct group, at least one 5 mm segment in 93 (70%) arteries was narrowed severely (76 to 100% in cross-sectional area) by atherosclerotic plaques, an average of 2.8 of 4.0 coronary arteries per patient; of the 112 major coronary arteries examined in the 28 patients in the unrecognized infarct group, 81 (72%) were so narrowed, an average of 2.9 of 4.0 coronary arteries per patient (p = NS). No significant difference was observed in the numbers of patients with severe narrowing of any of the 4 major arteries, or in the numbers of patients with 0 to 4 of the 4 major coronary arteries severely narrowed.

Quantitative analysis of amount of narrowing in 2,705 five mm long segments of the right, left anterior descending, and left circumflex coronary arteries (Fig. 1 and 2): Of the 1,443 five mm segments in the 33 patients in the recognized infarct group, 167 (12%) were narrowed 96 to 100% in cross-sectional area by atherosclerotic plaque; 444 (30%) were narrowed 76 to 95%; 519 (36%), 51 to 75%; 230 (16%), 26 to 50%; and 84 (6%), 0 to 25%. Of the 1,262 five mm segments of coronary artery in the 28 patients in the unrecognized infarct group, 91 (7%) were narrowed 96 to 100%; 461 (36%) were narrowed 76 to 95%; 374 (30%), 51 to 75%; 197 (16%), 26 to 50%; and 139 (11%), 0 to 25% (Fig. 1). There was no significant difference between the 2 groups in any of the 5 categories of cross-sectional area narrowing.

Within the recognized infarct group there was no significant difference in the percent of 5 mm segments of coronary artery with severe narrowing among the left anterior descending, left circumflex, or right coronary arteries (39, 41, and 46%, respectively) (Fig. 2). In the unrecognized infarct group, however, the right coronary artery had a significantly greater percent of 5 mm segments narrowed severely than the left anterior descending ($p < 0.02$) and left circumflex coronary arteries ($p < 0.03$) (55, 33, and 41%, respectively). There was no significant difference between the 2 groups in the per-

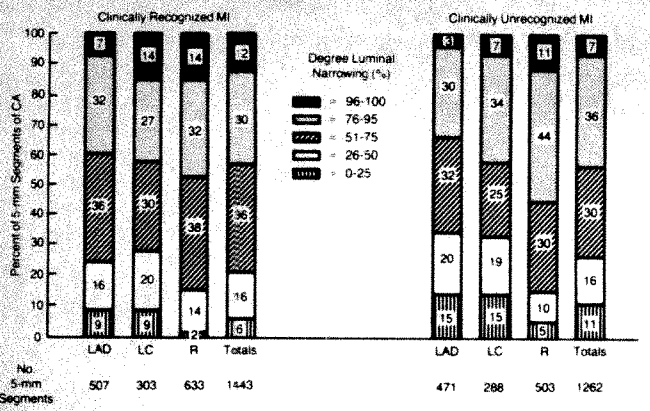

FIGURE 1. Percent of 5 mm segments of the right (R), left anterior descending (LAD), and left circumflex (LC) coronary arteries (CA) narrowed to various degrees by atherosclerotic plaque in 33 patients with clinically recognized and in 28 patients with clinically unrecognized acute myocardial infarction (MI) and healed transmural infarction at necropsy.

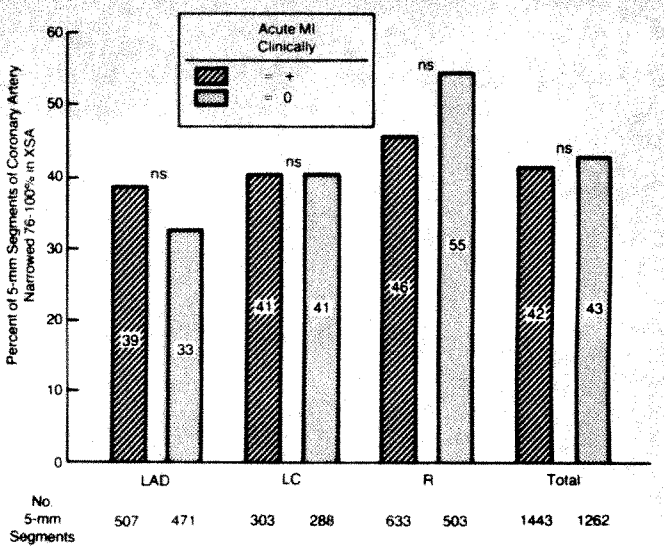

FIGURE 2. Percent of 5 mm segments of the right (R), left anterior descending (LAD), and left circumflex (LC) coronary arteries narrowed 76 to 100% in cross-sectional area (XSA) by atherosclerotic plaque in 33 patients with and in 28 patients without a clinical history of acute myocardial infarction (MI) and a healed transmural infarction at necropsy.

cent of 5 mm segments narrowed severely in each of the 3 major coronary arteries.

A scoring system was utilized to indicate both the severity and extent of coronary narrowing. Every 5 mm long segment of coronary artery from each patient was assigned a score of 1 to 4 based on the amount of cross-sectional area narrowing by atherosclerotic plaque as follows: 1 = 0 to 25% narrowing; 2 = 26% to 50%; 3 = 51 to 75%; and 4 = 76 to 100%. A total score was obtained for each patient and the score per 5 mm segment was then calculated by dividing the total score per patient by the number of 5 mm segments examined from the patient. The scores per 5 mm segment ranged from 1.8 to 3.9 (mean 3.2) in the recognized infarct group and from 1.9 to 3.7 (mean 3.1) in the unrecognized infarct group (p = NS).

Comments

Considerable controversy exists regarding the incidence and, in fact, the very existence of the entity that has been variously referred to as *unrecognized silent, undiagnosed, painless, asymptomatic,* or *inapparent* myocardial infarction. Some investigators[11,15] have suggested that a careful history taken within a short time of the acute myocardial infarct from a "... nonpsychotic, nonsenile, and nonmedicated..." individual will always disclose some symptom that in retrospect indicates that infarction had occurred. Necropsy studies have been particularly questioned because of the utilization of historic material obtained by nonprimary physicians who usually had not carefully questioned the patient about symptoms referable to the cardiovascular system.

Because of these difficulties, in the present analysis necropsy patients with healed transmural myocardial infarct were divided into clinically recognized and clinically unrecognized infarct groups by asking the question: was there a clinical history of hospitalization for suspected acute myocardial infarction with subsequent laboratory confirmation? Patients in whom this was the case were included in the recognized infarct group. The history of the remaining patients was further analyzed to exclude from the unrecognized infarct group those patients who reported some clinical event with or without hospitalization (such as change in pattern of chest pain, or acute worsening of congestive heart failure or syncope) that occurred more than 2 months before death that might have represented an atypical yet symptomatic acute myocardial infarction. Obviously, the latter analysis is still subject to variability in history-taking and history-giving abilities, patient recall, and variability in a patient's symptom threshold and does not exclude the stoic patient who for whatever reason does not report his symptoms or seek hospitalization. With these reservations in mind and by excluding all patients with an equivocal or inadequate history, we believe it valid to determine whether the 2 groups of patients just defined differed in clinical or necropsy findings, with particular emphasis on infarct size and location and amount and extent of coronary narrowing.

Clinical differences between clinically recognized and unrecognized infarct group: Previous studies have suggested that patients with clinically unrecognized compared with those with clinically recognized acute myocardial infarction have angina pectoris less frequently and that patients with angina pectoris rarely have clinically unrecognized infarcts.[2,3,5-7] In the present study, 21% of the patients in the unrecognized infarct group had typical angina pectoris compared with 42% of those in the recognized infarct group. This difference approached but did not achieve statistical significance ($0.05 < p < 0.10$). In ad-

dition, the incidence of fatal acute myocardial infarction was similar in both groups (25 and 24%, respectively). Thus, patients with a clinically unrecognized acute myocardial infarction that healed had an incidence of symptomatic myocardial ischemic events (fatal acute infarction or angina pectoris) which did not differ significantly from that in patients in whom the acute myocardial infarction was clinically recognized.

Some [5,7,16,17] but not all[2] investigators have reported an association between diabetes mellitus and clinically unrecognized or painless acute myocardial infarction. The present study supports that relationship by showing a significantly increased incidence of diabetes mellitus among the patients in the unrecognized infarct group (43%) compared with those in the recognized infarct group (15%).

Differences in location and extent of infarction: Johnson et al.[2] reported that subendocardial infarcts were less often clinically recognized than transmural infarcts. In addition, they found that among patients with subendocardial infarcts, those in the lateral and posterior walls of the left ventricle were less often recognized than those involving the anterior wall, and among patients with transmural infarcts, those in the lateral wall were less often clinically recognized than those in the anterior or posterior walls. These results are difficult to compare with those in the present study because of differing definitions of the terms *subendocardial* and *transmural* and differing methods of describing infarct locations. The present study includes only patients with healed transmural myocardial infarcts (involving greater than 50% of the thickness of the left ventricular wall at any point), which includes many patients who according to the definitions used by Johnson et al.[2] would be considered to have subendocardial infarcts (involving ". . . predominantly [*but not exclusively*] the endocardial half of the left ventricle"). In our necropsy experience, healed myocardial infarction limited to the endocardial half of the left ventricular wall is unusual, and if the infarct involves any portion of the epicardial half of the wall in addition to involvement of the subendocardial half, we consider it transmural. In addition, all but 3 of our 61 patients had infarction predominantly involving the anterior or posterior wall of the left ventricle with or without involvement of the lateral wall or the ventricular septum. Anterior wall infarction was significantly more common in the patients with recognized than unrecognized infarcts (48 versus 18%), while posterior wall infarction was more common in patients with unrecognized than in those with recognized infarcts (79 versus 45%). Among patients with clinically recognized infarction, the incidence of anteriorly and posteriorly located infarcts was similar (48 and 45%), while among those with clinically unrecognized infarction, posteriorly located scars were far more common than anteriorly located scars (79 versus 18%).

The size of the myocardial infarct in patients with unrecognized versus those with recognized infarct has not been previously reported. The mean percentage of left ventricular wall replaced by scar was significantly smaller in our patients with unrecognized than in those with recognized infarction (7 versus 17%).

Severity and extent of coronary artery narrowing: The amount and extent of coronary narrowing by atherosclerotic plaque in the entire lengths of the 4 major epicardial coronary arteries were examined qualitatively and quantitatively in all 61 patients, and no significant difference between the 2 study groups was observed. The patients with unrecognized or recognized infarcts had a similar mean number of coronary arteries narrowed severely (76 to 100% in cross-sectional area) (2.9 versus 2.8 of 4.0), a similar incidence of severe narrowing of the left main coronary artery (29 versus 18%), a similar overall percent of severely narrowed 5 mm coronary segments (43 versus 42%), and a similar percent of severely narrowed 5 mm segments of the left anterior descending, left circumflex, and right coronary arteries. To our knowledge, this information on clinically unrecognized infarct patients is not available elsewhere.

In summary, our necropsy patients with clinically unrecognized compared with those with clinically recognized healed transmural infarcts had similar incidences of angina pectoris and fatal acute myocardial infarction and higher incidences of diabetes mellitus and noncardiac causes of death, smaller infarcts more often located in the posterior wall of left ventricle, and similarly severe and extensive coronary narrowing by atherosclerotic plaque.

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Anatomic and Prognostic Implications of an Early Positive Treadmill Exercise Test

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Eighty men (group A) with clinical coronary artery disease underwent coronary angiography regardless of symptoms and previous therapy because they had a positive treadmill exercise test in stage I or II of the Bruce protocol. Thirty-four other men (group B) who also had an early positive treadmill test underwent coronary angiography because they had disabling angina pectoris despite medical therapy. We found left main coronary artery stenosis of 50% or greater of the vessel diameter in 28% of group A and 35% of group B ($p > 0.3$). In contrast, only 10% of 93 other catheterized patients who had treadmill tests that were not early positive had left main coronary disease ($p < 0.001$). Fifty-four patients from group A who did not have left main stenosis of 50% or greater were treated medically. In this subgroup, 85% had 2 or 3 major coronary vessels with 75% or greater stenosis. These patients had a 36 month survival rate of 89.2%.

We conclude that an early positive treadmill test identifies patients who have an increased likelihood of having left main coronary stenosis, even if they are minimally symptomatic. To identify left main coronary stenosis, catheterization may be justified in patients whose angina pectoris has been mild or not intensively treated when they have an early positive treadmill response. After left main coronary stenosis has been excluded, these patients may be treated medically with a low mortality.

Aortocoronary bypass surgery improves survival in symptomatic patients with left main coronary artery disease.[1-8] For this reason, investigators have attempted to find noninvasive tests that will identify patients with significant narrowing of the left main coronary artery.[9] Retrospective studies of patients who underwent cardiac catheterization because of severe angina pectoris have found an association between an ischemic electrocardiographic response in the early stages of treadmill exercise testing and significant left main coronary stenosis.[10-15] This association would be important clinically if it could be confirmed prospectively in patients with mild angina pectoris who might not ordinarily be considered candidates for coronary angiography and aortocoronary bypass surgery.[16]

An ischemic electrocardiographic response at low levels of exercise has also been reported to identify a subgroup of patients who have a poor prognosis on medical therapy.[12,17-19] This has led some clinicians[20] to use the treadmill test result, even after the coronary anatomy and left ventricular function are defined, as an indication that aortocoronary bypass surgery should be performed. However, a recent study[21] found that patients who had marked S-T segment depression during treadmill exercise, even in its early stages, could be treated medically with a low mortality.

In the present study we performed cardiac catheterization in 80 patients who had an exercise test that was positive in stage I or II of the Bruce protocol but who did not have angina pectoris that was refractory to medical therapy. We compared this study group with a group of patients who had angina pectoris that was refractory to medical therapy and who also had stage I or II positive

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treadmill tests. Our purpose was to determine (1) the predictive value of an early positive treadmill response for left main coronary stenosis in patients who were selected for cardiac catheterization because of an early positive treadmill response at a time when they were not already considered clinically to be candidates for aortocoronary bypass therapy, and (2) the prognosis on medical therapy of patients in this group who were found at catheterization not to have significant left main stenosis.

Methods

Study population: Between January 1977 and December 1978, 378 patients with a clinical diagnosis of coronary artery disease underwent 391 cardiac catheterizations. Of these patients, 358 had not previously undergone aortocoronary bypass surgery. Treadmill exercise tests were performed before catheterization in 207 patients. Exercise tests were not generally performed in patients with severe angina pectoris who were already being considered for aortocoronary bypass surgery because of an unsatisfactory response to medical treatment. One hundred fourteen patients had an early positive treadmill test, that is, an ischemic electrocardiographic response to treadmill exercise in stage I or stage II of the Bruce protocol. These 114 patients constitute the study population.

The study population was divided by prospective definition into 2 groups. Group A consisted of 80 men who were catheterized because their treadmill tests became positive in stage I (37 patients) or stage II (43 patients). None of these patients had angina pectoris that had been shown to be refractory to medical management. All of them had angina pectoris or electrocardiographic evidence of a previous myocardial infarction (0.04 second Q waves), or both. Before 1977 these patients would not have been considered candidates for cardiac catheterization at our institution because they had minimal symptoms or had not yet had an adequate trial of medical therapy. They were offered cardiac catheterization because previous data obtained in patients with medically refractory angina suggested that an early positive treadmill response predicts an increased risk of left main coronary stenosis.[12]

Group B consisted of 34 men who also had stage I (19 patients) or stage II (15 patients) positive treadmill tests, but who were catheterized because (1) they had severe angina pectoris, defined as New York Heart Association[22] functional class III or IV, and (2) they had received an adequate trial of medical therapy, defined as a combination of propranolol (more than 160 mg/day, unless there was documented intolerance to this dose) and long-acting nitrates. Until the first patients were recruited into this study in 1977, our primary indication for cardiac catheterization in coronary artery disease was disabling angina pectoris that had not responded to medical management. Group B, therefore, represented a group of patients who were selected for cardiac catheterization by criteria that were similar to those used in previous studies of exercise testing at this and other institutions.[12,16]

Treadmill exercise tests: Graded treadmill exercise tests were performed according to the Bruce protocol.[23] Exercise stages lasted 3 minutes. Treadmill exercise in stage I was performed at 1.7 miles/h and a 10% incline, with an estimated energy expenditure of 4 to 4.5 METS (multiples of resting oxygen consumption). Exercise in stage II was performed at 2.5 miles/h and a 12% incline, with an estimated energy expenditure of 7 METS. Exercise was submaximal and was terminated when criteria for a positive response were met or when the heart rate exceeded 85% of the maximum heart rate predicted for the patient's age, if exhaustion or severe symptoms did not occur first.

TABLE I Study Population

	Group A		Group B	
	n	%	n	%
n	80	...	34	...
Age (yr) (mean ± SD)	53 ± 6	...	52 ± 8	...
Previous myocardial infarction	22	28	8	24
NYHA functional class (angina)				
I	8	10	0	...
II	26	33	0*	...
III	23	29	12	35
IV	23	29	22*	65
No therapy	36	45	0*	...
Propranolol (mg/day)				
≤160	25	31	3†	9
>160	6	8	31*	91
Long-acting nitrates	23	29	33*	97

* $p < 0.001$ compared with group A.
† $p < 0.02$ compared with group A.
NYHA = New York Heart Association; SD = standard deviation.

A positive response to exercise was defined as (1) J point depression of at least 0.1 mV below the P-R segment associated with a horizontal or downsloping S-T segment of 0.08 second duration (in the presence of 0.05 mV or greater J point depression in the control tracing, additional depression of at least 0.2 mV was required), or (2) S-T elevation of at least 0.1 mV above baseline. Precordial leads V_4, V_5, and V_6 were continuously monitored during exercise. A standard 12 lead electrocardiogram was performed at the end of each minute of exercise and repeated every 2 minutes after exercise was terminated for a minimum of 6 minutes or until changes had returned to baseline. Patients whose electrocardiograms became positive during the recovery period were considered positive at the stage in which they had terminated exercise.

Cardiac catheterization: Right and left heart catheterization was performed in all patients using the Judkins technique.[24] Hemodynamic measurements were routinely made before cineangiography. Cardiac output was calculated by the Fick method,[25] and left ventricular ejection fraction was determined by planimetry using the single plane right anterior oblique view.[26] Coronary angiograms were performed in multiple left anterior oblique and right anterior oblique projections. A stenosis that reduced the luminal diameter by 75% or more was considered significant, except in the left main coronary artery, where a stenosis of 50% or more was defined as significant.

Follow-up: Decisions regarding patient management after cardiac catheterization were made by referring physicians, who also provided subsequent medical care. Follow-up information for group A was obtained 6 months and annually after cardiac catheterization, and finally in September 1981, either by a staff cardiologist during a clinic visit or by a research associate by telephone. The follow-up was complete in all 80 patients. At each evaluation, if there was suspicion of myocardial infarction, hospital records were reviewed or personal physicians were contacted for corroborating electrocardiographic or enzymatic evidence. When a patient died, a description of the cause and circumstances was sought from the hospital record, the private physician, or a family member. Most patients in group B underwent aortocoronary bypass surgery; their follow-up data will not be presented.

Data analysis: Differences between patient groups in clinical, angiographic, and treadmill variables were evaluated

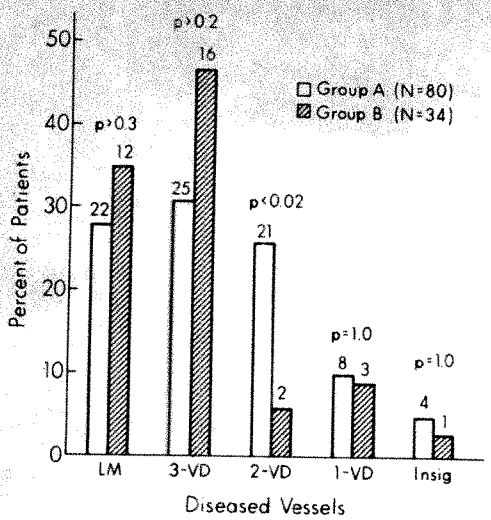

FIGURE 1. Coronary arteriographic findings in groups A and B. Absolute numbers of patients are **above the bars,** as are p values comparing group A and B patients. Insig = insignificant coronary disease; LM = left main coronary lesions of 50% or greater; excluding patients with left main stenosis of 50% or greater, 3-VD = 3 vessel disease, 2-VD = 2 vessel disease, and 1-VD = 1 vessel disease.

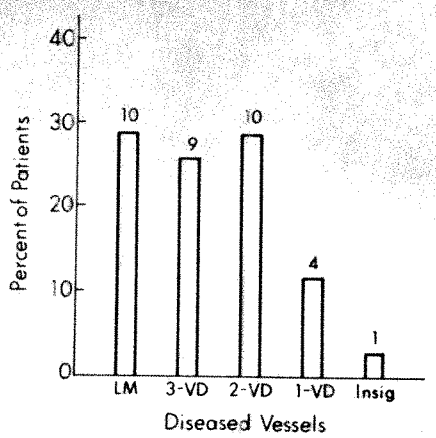

FIGURE 2. Coronary arteriographic findings in 34 group A patients with New York Heart Association angina pectoris class I and II. Absolute numbers of patients are **above the bars.** The percentages of patients did not differ from those in group A as a whole (p >0.3 for each anatomic category). Abbreviations as in Figure 1.

by contingency table analyses utilizing chi-square tests of significance or, when patient numbers were small, Fisher's exact test. Hemodynamic variables were examined between groups by a 1 way analysis of variance. Cumulative survival rates after cardiac catheterization were computed by the method of Kaplan and Meier.[27] Medically treated patients who subsequently underwent surgery were withdrawn from the medical group in the month of their operation.

Results

Study population (Table I): Groups A and B did not differ significantly in mean age or number of patients with a previous myocardial infarction. The distribution of functional classes for angina pectoris and the extent of antianginal therapy were substantially different in groups A and B as a result of the criteria used for patient enrollment (see Methods).

Cardiac catheterization findings (Fig. 1): Thirty-four of our 114 patients (30%) had significant left main coronary artery stenosis, including 22 patients (28%) in group A and 12 patients (35%) in group B (p >0.3). Twenty-two of these 34 patients (19% of our study population) had left main stenosis that reduced the luminal diameter by at least 75%, with 15 (19%) in group A and 7 (21%) in group B (p = 1.0).

Among our 80 patients without significant left main coronary stenosis, 25 patients (31%) in group A had 3 vessel disease, compared with 16 patients (47%) in group B (p >0.2). Group A had more 2 vessel disease than group B (26% versus 6%, p <0.02; this p value must be interpreted with caution because of the number of tests already performed on the study population). Similar percentages of patients in each group had 1 vessel disease and insignificant coronary disease.

In patients with significant coronary artery lesions, left ventricular end-diastolic pressure was 14.6 ± 6.6 (mean ± standard deviation) mm Hg in group A and 15.2 ± 6.8 in group B; the mean cardiac index was 2.71 ± 0.36 liters/min/m^2 in group A and 2.69 ± 0.43 in group B; and the mean ejection fraction was 60 ± 14% in group A and 59 ± 13 in group B. These differences were not statistically significant.

Coronary anatomy in functional class I and II patients (Fig. 2): Thirty-four patients in group A who were in class I (8 men) or class II (26 men) for angina pectoris at the time of their early positive treadmill tests and cardiac catheterization were examined separately. Ten patients (29%) had significant left main coronary stenosis; 7 (21%) had stenosis of 75% or greater of the vessel diameter.

Coronary anatomy in other exercised patients (Fig. 3): Ninety-three of the 207 patients who had treadmill test evaluation before cardiac catheterization had test results that were not positive early in exercise. Only 9 patients (10%) had significant left main coronary stenosis (p <0.001 compared with groups A and B combined); these included 1 of 21 patients who had a negative test, 4 of 50 patients who had an indeterminate test, and 4 of 22 patients who had a test that became positive in stage III or later. Only 6 patients (6%) had left main coronary stenosis of 75% or greater of the vessel diameter (p <0.01 compared with groups A and B combined). One vessel coronary disease and insignificant disease were found more frequently in the group of exercised patients whose tests were not early positive than in those in study groups A and B (Fig. 3).

Coronary anatomy predicted by treadmill test variables: In order to assign a predictive value to early positive treadmill tests, we divided the number of patients with early positive treadmill tests into the number of those same patients with left main coronary stenosis, 3 vessel disease, and either left main stenosis or 3 vessel disease; the resulting predictive values for group A patients were 28% for left main stenosis, 31% for 3 vessel

TABLE II Coronary Anatomy Predicted by Treadmill Variables*

Variable	n	Left Main (n = 22)	3-VD (n = 25)	Left Main or 3-VD (n = 47)
Onset of S-T changes				
Stage I	37	12 (32)	16 (43)	28 (76)
Stage II	43	10 (23)	9 (21)	19 (44)
Onset in recovery period	9	3 (33)	3 (33)	6 (67)
Maximum stage reached				
Stage I	24	9 (38)	8 (33)	17 (71)
Stage II	44	9 (20)	17 (39)	26 (59)
Extent S-T depression				
≥0.2 mV	45	15 (33)	12 (27)	27 (60)
≥0.3 mV	23	8 (35)	8 (35)	16 (70)
Slope S-T depression				
Horizontal	57	18 (32)	13 (23)†	31 (54)†
Downsloping	14	4 (29)	5 (36)	9 (64)
S-T elevation‡	13	2 (15)	7 (54)	9 (69)
Leads with S-T change				
≥3 leads	60	19 (32)	20 (33)	39 (65)
≥6 leads	20	6 (30)	7 (35)	13 (65)
HR ≤120 beats/min	34	10 (29)	13 (38)	23 (68)
Time until S-T recovery				
≥2 minutes	60	17 (28)	16 (27)§	33 (55)§
≥6 minutes	28	10 (36)	7 (25)	17 (61)

* Numbers in parentheses indicate predictive value (in percent) of each exercise variable for each anatomic description. No variable had a predictive value statistically greater than the stage I or II onset of S-T changes alone.
† Treadmill recordings unavailable for analysis in 1 patient.
‡ Several patients had both S-T elevation and S-T depression in different leads.
§ Treadmill recordings inadequate for analysis in 2 patients.
HR = heart rate; left main = significant left main coronary stenosis; 3-VD = 3 vessel disease (excluding left main patients).

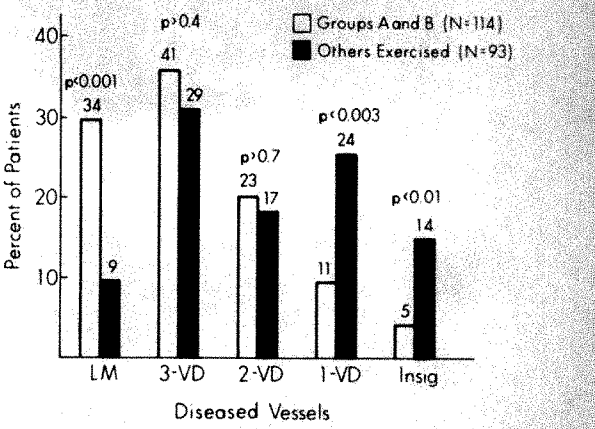

FIGURE 3. Coronary arteriographic findings in combined groups A and B compared with other exercised patients who did not have an early positive treadmill test. Absolute numbers of patients are **above the bars,** as are p values comparing the 2 populations. Abbreviations as in Figure 1.

disease, and 59% for left main or 3 vessel disease. We also determined the predictive values of 8 other treadmill variables in group A (Table II) and group B; none was a statistically significant improvement over the early positive treadmill test.

Follow-up data: We followed up the 54 patients from group A who had significant coronary disease that did not involve the left main coronary artery for up to 53 months (median 36 months). Forty-six patients (85%) had multivessel coronary artery disease, including 25 (46%) patients with 3 vessel and 21 (39%) with 2 vessel disease. Twelve patients (22%) had a left ventricular ejection fraction less than 50%.

All 54 patients were initially treated medically; 12 (22%) underwent aortocoronary bypass surgery 1 week to 40 months (median 12 months) after catheterization because of the development of disabling angina pectoris refractory to antianginal therapy. Seven of these patients had a second cardiac catheterization before surgery.

Five of the 42 patients who were medically treated for the duration of the study died, 4 from myocardial infarction 8, 17, 28, and 31 months after cardiac catheterization, and 1 from unknown cause 9 months after catheterization. There were no other episodes of myocardial infarction among medically treated patients. Kaplan-Meier estimates of survival probability were 98.0 ± 2.0% (± standard error of the estimate) at 8 months, 96.0 ± 2.8% at 9 months, 93.8 ± 3.5% at 17 months, 91.5 ± 4.1% at 28 months, and 89.2 ± 4.6% at 31 months (Fig. 4).

The 22 patients from group A who had significant left main coronary stenosis were followed up for up to 58 months (median 45 months). Fourteen patients (64%) underwent aortocoronary bypass surgery 1 week to 5 months (median 3 weeks) after catheterization. One patient died from unknown cause 2 months after surgery. One patient had a documented myocardial infarction 27 months after surgery. Thirteen patients who had surgery survived the follow-up period.

Eight patients with significant left main coronary stenosis were treated medically. One died from an acute myocardial infarction 33 months after catheterization. The remaining 7 patients survived the follow-up period.

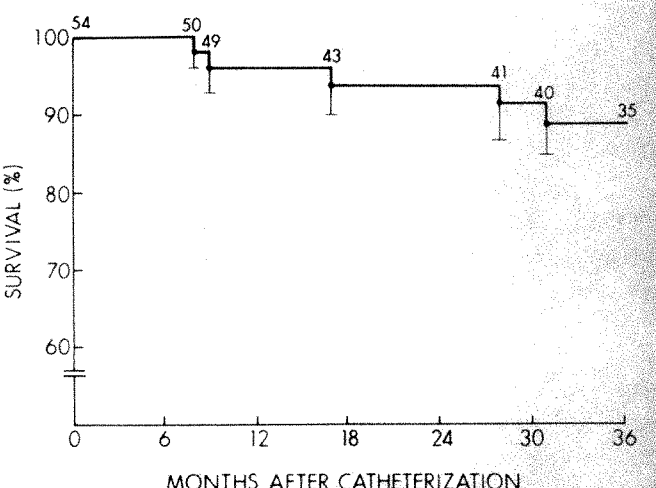

FIGURE 4. Kaplan-Meier estimates of probability of survival in patients with coronary artery disease catheterized because of an early positive treadmill test (group A), excluding patients with significant left main stenosis. Standard errors of the estimates are indicated. **Numbers above the graph** indicate patients at risk.

Discussion

Anatomic findings: The survival of patients with coronary artery disease depends on the extent and distribution of stenotic lesions and on the overall function of the left ventricle.[28–33] Significant stenosis of the left main coronary artery has a poor prognosis,[34–39] which may be substantially improved by aortocoronary bypass surgery.[1–8] Published series have reported significant left main stenosis in 2.6 to 9% of patients with coronary disease.[31,34,36,38,40] The patients in these series generally underwent cardiac catheterization because they were highly symptomatic. However, among 156 asymptomatic or mildly symptomatic patients with coronary artery disease who were evaluated at the National Institutes of Health,[41] a comparable 10% had significant left main stenosis.

Prediction of left main coronary disease by exercise testing: Several retrospective investigations[10–15] have shown that an ischemic electrocardiographic response to treadmill exercise can predict left main coronary stenosis in symptomatic patients. McNeer et al.[12] demonstrated that 27% of patients with a positive test who stopped treadmill exercise in stage I and 24% of those who stopped in stage II had significant left main stenosis. Weiner et al.[10] found that 0.2 mV or greater downsloping S-T depression beginning in stage I, lasting at least 6 minutes into the recovery period, and involving at least 5 electrocardiographic leads had a 32% predictive value for significant left main stenosis. We found a 35% predictive value for left main disease in our patients with medically refractory and disabling angina pectoris (group B) by relying simply on the onset of a positive S-T segment response in treadmill stage I or II.

In our prospective study, we found left main coronary disease in 28% of our patients catheterized because of an early positive treadmill test (group A), which confirms that patients with an ischemic electrocardiographic response at low levels of exercise have an increased likelihood of having left main disease. This conclusion appears equally valid in the subgroup of patients with class I or II angina pectoris, 29% of whom had left main disease. Similar results were reported by Epstein et al.,[41] who found that 32% of their asymptomatic or mildly symptomatic patients who had S-T depression of 0.2 mV or greater during treadmill exercise also had significant left main stenosis. Blumenthal et al.[42] found that 35% of patients with class I or II angina pectoris who met any 1 of 6 criteria for a "strongly positive" treadmill test had left main disease.

Recent data indicate that the poor outcome associated with medically treated left main coronary disease may be limited to patients whose lesions reduce the luminal diameter by more than 75%.[40,43] Left main stenosis meeting this criterion was present in 19% of all patients with an early positive treadmill test and in 21% of the subgroup of group A with class I or II angina pectoris.

We compared cardiac catheterization findings in groups A and B to determine whether substantial group differences in symptoms of angina pectoris would translate into differences in distribution of coronary disease and in ventricular function. Instead, we found that these 2 populations of patients had similar hemodynamic function and ejection fractions and similar incidences of significant left main and 3 vessel coronary artery disease.

Combining groups A and B results in a total of 114 patients who had early positive treadmill tests. Thirty % of these patients had significant left main stenosis, compared with only 10% of the 93 other exercised patients ($p < 0.001$, Fig. 3). This comparison indicates that in our catheterized population, an early positive exercise test selected patients who were 3 times more likely to have left main disease than were those whose treadmill tests were not positive early.

Many other variables of the treadmill test have been reported to be useful for identifying patients with an increased likelihood of having left main stenosis.[44–48] We attempted retrospectively to enhance the ability of the early positive treadmill test to predict significant left main or 3 vessel disease by individually analyzing other exercise variables, but we could identify no single variable that improved the predictive value of the early positive test. It is possible that combinations of variables might have resulted in a higher predictive value, or that individual variables might have enhanced the predictive value of the exercise test in a larger patient population.

Prognostic findings: Several studies[12,17–19] have demonstrated that ischemic electrocardiographic responses early in exercise indicate a poor prognosis. McNeer et al.[12] retrospectively found that a positive treadmill test in patients who were forced to stop exercise in stage I or II of the Bruce protocol identified a "high risk subgroup" with a 12 month cumulative survival rate of 85% and a 36 month survival rate of 69%. Follow-up of our 54 medically treated patients in group A without significant left main coronary stenosis revealed an estimated 12 month survival rate of 96.0% and a 36 month survival rate of 89.2%.

Important differences in these 2 patient populations may explain the disparity in survival. First, McNeer et al.[12] included medically treated patients with significant left main stenosis, while we excluded these patients. Second, the distribution of coronary anatomy and ventricular function may have been different. Third, the patients analyzed by McNeer et al. were catheterized because of severe symptoms but did not undergo aortocoronary bypass surgery. Some of these patients may have been rejected for surgery on the basis of clinical or anatomic factors with an adverse effect on survival.

Finally, the primary indications for cardiac catheterization were different in the 2 populations. Patients selected for angiographic evaluation because of disabling angina pectoris despite aggressive medical therapy may constitute a higher risk population than patients selected primarily on the basis of an early positive treadmill test. This clinical difference in the 2 populations may have important prognostic implica-

tions independent of the early positive exercise test and the anatomic severity of coronary artery disease and left ventricular dysfunction.

Some investigators have stated that in patients with known coronary anatomy, abnormal exercise responses provide important prognostic information[49] and indicate a need for aortocoronary bypass surgery.[20] However, recent investigations[29,50] suggest that exercise test variables may not contribute significantly to prediction of prognosis in coronary artery disease after multiple clinical and catheterization factors have been considered. A detailed analysis of 81 clinical and catheterization variables has shown that after a patient has been catheterized, the assessment of prognosis should be based on the coronary anatomy and ventricular function and not on treadmill test performance (Gibbons R, personal communication).

Podrid et al.[21] recently reported that 142 men with S-T segment depression greater than 0.2 mV during treadmill exercise had an annual mortality of 1.4%. A subgroup of 46 patients who exercised for 6 minutes or less had an annual mortality of 2.0%. Although these patients had clinical evidence of coronary artery disease, few had angiographic documentation of their disease. The authors of this study concluded that there is no need to resort to aortocoronary bypass surgery on the basis of a profoundly abnormal treadmill test alone.

Our study population differs from that of Podrid et al.[21] in that all patients had undergone elective cardiac catheterization. Our 36 month survival estimate of 89.2% yields an annual mortality of 3.6%. Taken together, the present investigation and the Podrid study suggest that medical management of patients with markedly abnormal treadmill exercise responses, even those with known severe coronary artery disease, is associated with a low mortality.

Dagenais et al.[51] found that among a catheterized and a noncatheterized population of patients who had S-T segment depression greater than 0.2 mV during treadmill testing, exercise duration identified subjects who had different survival rates. This issue cannot be addressed in the present study because the test protocol called for exercise to be terminated when criteria for a positive response were met or when the target heart rate was reached, unless exercise was first limited by symptoms.

This study is limited by the lack of a control population for group A to include patients who do not have early positive treadmill tests. We could not justify recommending cardiac catheterization to patients whose angina pectoris was mild or responsive to medical therapy, such as those in group A, when they did not have an early positive treadmill result. The 93 catheterized patients referred to in the Results section who had treadmill tests that were not positive early were identified retrospectively and are not an adequate control population. They were catheterized because of severe angina pectoris. They are included because they indicate the incidence of significant left main coronary disease (10%) in a population catheterized on the basis of severe symptoms.

Clinical implications: Our study confirms that a stage I or II positive treadmill test predicts an increased likelihood of significant left main coronary stenosis in patients with and without medically refractory, disabling angina pectoris. Furthermore, it indicates that an early positive exercise test has the same implication in patients who have mild angina pectoris or who are asymptomatic after myocardial infarction. These apparently stable patients have an increased incidence of presumably very threatening left main coronary disease, which justifies invasive evaluation.

In patients discovered to have left main stenosis, aortocoronary bypass surgery would be expected to improve prognosis. Once patients with early positive treadmill tests are demonstrated not to have significant left main disease, we believe they may be treated medically as long as their symptoms are adequately controlled by medication. These patients have had an excellent outcome over 3 years on conservative therapy, and functional impairment should continue to be the primary indication for surgical therapy in this group. An early positive treadmill result may not portend a high risk of mortality independent of the patient's functional status, the distribution of coronary disease, and the extent of ventricular dysfunction.

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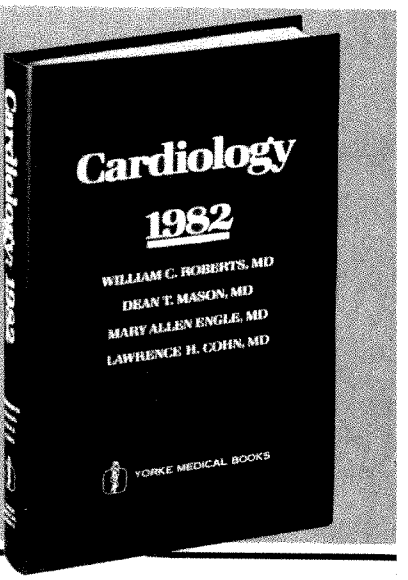

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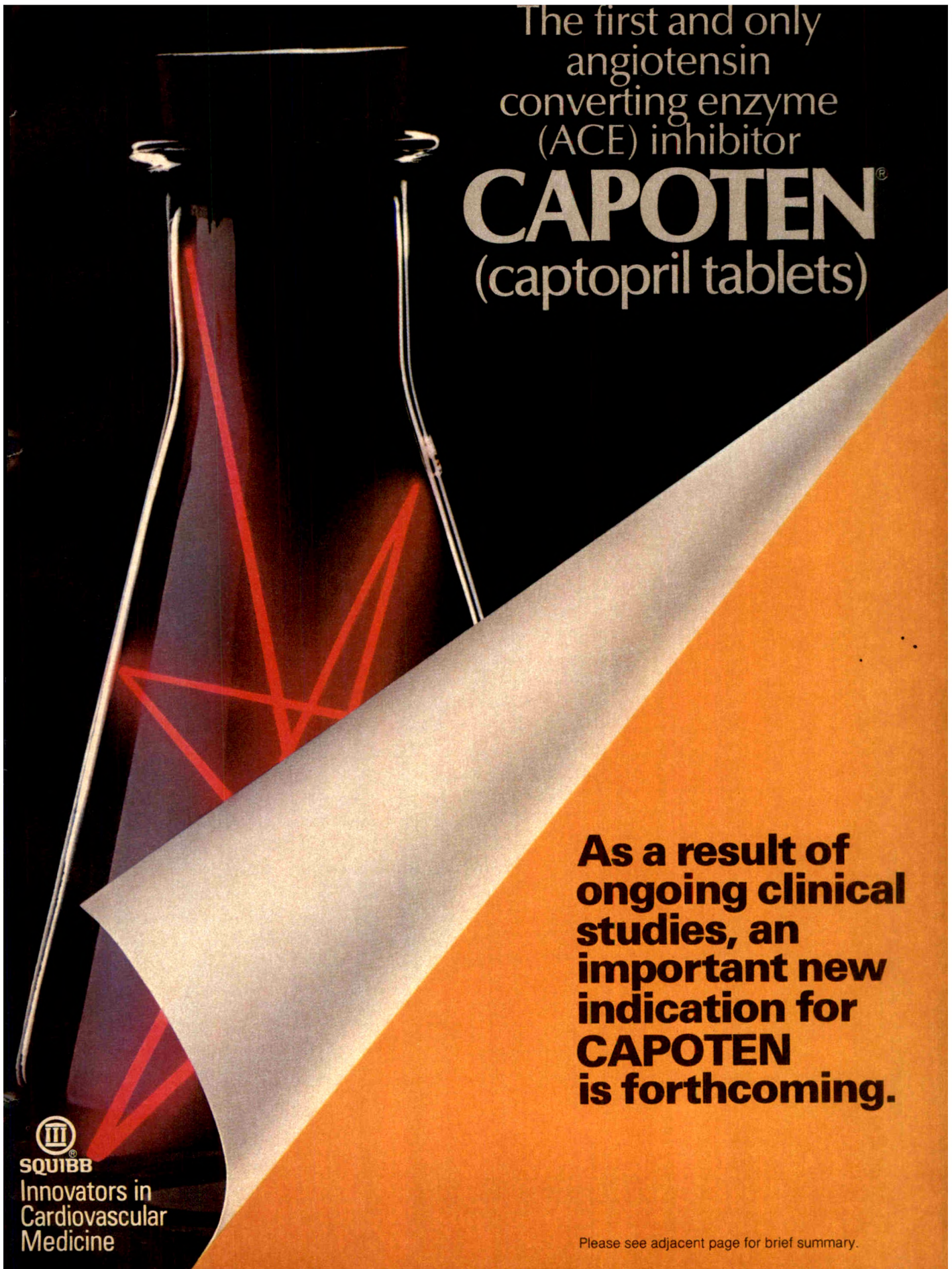
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DESCRIPTION: Capoten (captopril) is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for converting angiotensin I to angiotensin II.

INDICATIONS: Because serious adverse effects have been reported (see WARNINGS), Capoten is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects. Usually, multidrug regimens include combinations of a diuretic, a sympathetic nervous system-active agent (such as a beta-blocker) and a vasodilator.

Capoten (captopril) is effective alone, but in the population described above, it should usually be used in combination with a thiazide-type diuretic. The blood pressure lowering effects of captopril and thiazides appear to be additive.

WARNINGS: Proteinuria—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. Existence of prior renal disease increased the likelihood of development of proteinuria. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued, but some patients had persistent proteinuria. The BUN and creatinine were seldom altered in the proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related; this is uncertain since patients were not biopsied prior to treatment and membranous glomerulopathy may be associated with hypertension in absence of captopril therapy. Since most cases of proteinuria occurred by the 8th month of captopril therapy, patients on captopril should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis—Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller, and it is sufficient in these patients to have white blood cell counts every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in severely salt/volume depleted persons such as those treated vigorously with diuretics, e.g., patients with severe congestive heart failure (see PRECAUTIONS [Drug Interactions]).

PRECAUTIONS: General: *Impaired Renal Function*—Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible (see DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]). *Surgery/Anesthesia*—During major surgery or anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release; if hypotension occurs and is considered due to this mechanism, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy*—A precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretic therapy and those on severe dietary salt restriction or dialysis. The possibility of hypotensive effects can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose. If hypotension occurs, place the patient in a supine position and, if necessary, administer an I.V. infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Since captopril decreases aldosterone production, elevation of serum potassium may occur. Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. If the patient has received spironolactone at any time up to several months prior to captopril therapy, determine the serum potassium frequently since the effect of spironolactone persists.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential.

Animal Toxicology: Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and variation of retinal blood vessels. Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses 50 to 150 times the maximum recommended human dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8 to 30 times MRHD. The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8 to 30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 and 30 times MRHD and thrombocytopenia at 30 times MRHD. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacri-

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30 times MRHD, bone marrow suppression was found to be reversible upon conti drug administration. Captopril caused hyperplasia of the juxtaglomerular apparatus c kidneys at doses 7 to 200 times the MRHD in rats and mice, at 20 to 60 times M in monkeys, and at 30 times the MRHD in dogs. Gastric erosions/ulcerations wer creased in incidence at 20 and 200 times MRHD in male rats and at 30 and 65 times M in dogs and monkeys, respectively. Rabbits developed gastric and intestinal ulcers given oral doses about 30 times MRHD for only 5 to 7 days. In the two-year rat study, versible and progressive variations in the caliber of retinal vessels (focal saccula and constrictions) occurred at all dose levels (7 to 200 times MRHD) in a dose-re fashion. The effect was first observed in the 88th week of dosing, with a progress increased incidence thereafter, even after cessation of dosing.

Pregnancy: Category C—Captopril was embryocidal in rabbits when given in doses 2 t times (on a mg/kg basis) the maximum recommended human dose. The marked bryocidal effect in rabbits was most probably due to the particularly marked decr in blood pressure caused by the drug in this species. Captopril given to pregnant ra 400 times the recommended human dose continuously during gestation and lacta reduced neonatal survival. No teratogenic effects (malformations) have been seen large doses of captopril in hamsters, rats, and rabbits.

There are no adequate and well-controlled studies in pregnant women. Capt should be used during pregnancy only if the potential benefit justifies the potential to the fetus.

Nursing Mothers: Concentrations of captopril in human milk are about 1% of thos maternal blood. The effect of low levels of captopril on the nursing infant has not b determined. Exercise caution when administering captopril to a nursing woman, anc general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established altho there is limited experience with use of captopril in children from 2 months to 15 y of age with secondary hypertension and varying degrees of renal insufficiency. Dosi on a weight basis, was comparable to that used in adults. Captopril should be use children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving at 4000 patients.

Renal—One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal sufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 pati but relationship to drug use is uncertain.

Hematologic—Neutropenia/agranulocytosis (probably drug related) occurred in at 0.3% of captopril treated patients (see WARNINGS). Two of these patients develo sepsis and died.

Dermatologic—Rash (usually maculopapular, rarely urticarial), often with pruritus sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 4 weeks of therapy. The rash is usually mild and disappears within a few days of dos reduction, short-term treatment with an antihistaminic agent, and/or discontinuing t apy; remission may occur even if captopril is continued. Pruritus, without rash, in at 2 of 100 patients. Between 7 and 10% of patients with skin rash have shown an eosi philia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, photosensitivity have also been reported. Angioedema of the face, mucous membra of the mouth, or of the extremities in about 1 of 100 patients—reversible on disconti ance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor 2 to 5 of 1000 patients.

Cardiovascular—Hypotension in about 2 of 100 patients. See PRECAUTIONS (D Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycar chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocar infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1 patients.

Dysgeusia—About 7 of 100 patients developed a diminution or loss of taste perc tion; taste impairment is reversible and usually self-limited even with continued drug (2 to 3 months). Weight loss may be associated with the loss of taste. Gastric irritati abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulce peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, a paresthesias reported in about 0.5 to 2% of patients but did not appear at increas frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although causal relationship has been established. A single case of hepatocellular injury w secondary cholestasis has been reported in association with captopril use. A transi elevation of BUN and serum creatinine may occur, especially in volume-depleted or ren vascular hypertensive patients. In instances of rapid reduction of longstanding or sever elevated blood pressure, the glomerular filtration rate may decrease transiently, al resulting in transient rises in serum creatinine and BUN. Small increases in serum pota sium concentration frequently occur, especially in patients with renal impairment (s PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with I.V. infusion of normal saline is the treatment of choice for restoration of blood pre sure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour befo meals. Dosage must be individualized.

Give consideration to recent antihypertensive drug therapy, extent of blood pressu elevation, salt restriction, and other circumstances before initiating therapy. If possibl discontinue the patient's previous antihypertensive drug regimen for one week befo starting captopril. Initial dose of CAPOTEN (captopril) is 25 mg t.i.d. If satisfactory bloo pressure reduction is not achieved after 1 or 2 weeks, dose may be increased to 50 m t.i.d. If the blood pressure has not been satisfactorily controlled after another 1 to 2 week add a modest dose of a thiazide-type diuretic (e.g., hydrochlorothiazide, 25 mg daily The diuretic dose may be increased at 1- to 2-week intervals until its highest usual an hypertensive dose is reached. If further blood pressure reduction is required, CAPOTE (captopril) may be increased to 100 mg t.i.d. and then, if necessary, to 150 mg t.i (while continuing the diuretic). The usual dose range is 25 to 150 mg t.i.d. A maximu daily dose of 450 mg CAPOTEN (captopril) should not be exceeded.

For patients with accelerated or malignant hypertension, when temporary discontinu tion of current antihypertensive therapy is not practical, or when prompt titration to mo normotensive blood pressure levels is indicated, current antihypertensive medication ma be stopped and CAPOTEN (captopril) dosage promptly initiated at 25 mg t.i.d., under clos medical supervision. The daily dose of CAPOTEN (captopril) may be increased every 2 hours until a satisfactory blood pressure response is obtained or the maximum captop dose is reached. In this regimen, addition of a more potent diuretic, e.g., furosemid may also be indicated. Beta-blockers may also be used in conjunction with captop therapy (see PRECAUTIONS [Drug Interactions]), but the effects of the 2 drugs are les than additive.

Dosage Adjustment in Renal Impairment—Because CAPOTEN (captopril) is excrete primarily by the kidneys, excretion rates are reduced in patients with impaired renal func tion. These patients will take longer to reach steady-state captopril levels and will reac higher steady-state captopril levels for a given daily dose than patients with normal ren function. Therefore, these patients may respond to smaller or less frequent doses. Ac cordingly, for patients with significant renal impairment, initial daily dosage of CAPOTE (captopril) should be reduced, and smaller increments utilized for titration, which shoul be quite slow (1- to 2-week intervals). After desired therapeutic effect has been achieve dose should be slowly back-titrated to determine minimal effective dose. When con comitant diuretic therapy is required, a loop diuretic (e.g., furosemide), rather than thiazide diuretic, is preferred in patients with severe renal impairment.

For full prescribing information, consult package insert.

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and i UNIMATIC® unit-dose packs of 100 tablets.

When patients need more potassium than tablets can easily offer...

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Consider the simplicity of KLORVESS® EFFERVESCENT GRANULES

Each packet (2.8 g) provides 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, and L-lysine monohydrochloride 0.913 g.

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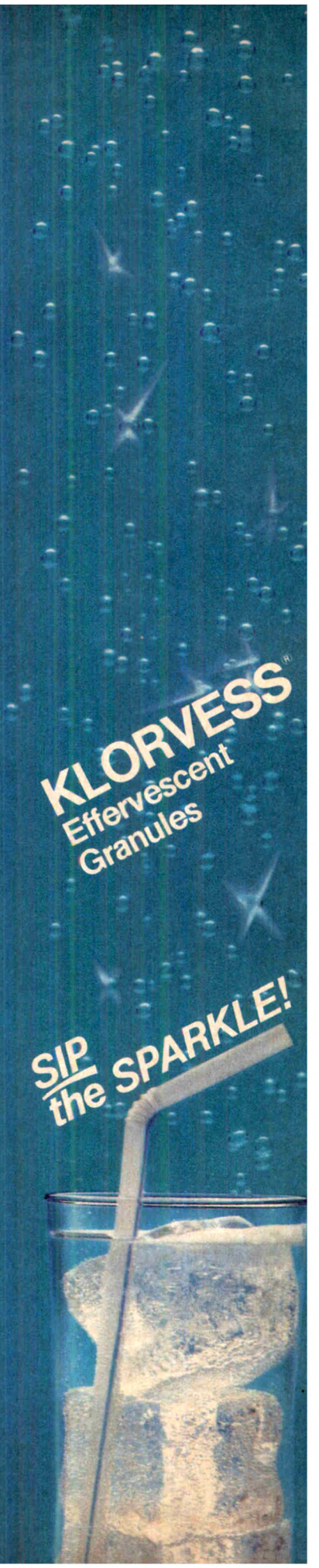

Give your patients the KLORVESS® sparkle

Klorvess® Effervescent Granules and Klorvess® (potassium chloride) 10% Liquid

Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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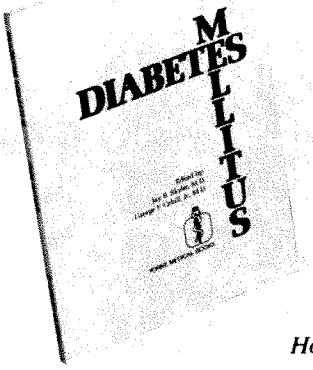

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A letter on the importance of building a medically aware public

Pfizer

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Dear Doctor:

Scientific progress continues to result in significant new therapeutic advances. As you know, the positive results achieved with these treatments depend in good measure upon effective physician/patient communication. At the same time, there is a growing interest by the general public in becoming better informed on healthcare issues and in assuming a larger role in maintaining their own health. We believe that an informed patient has a better chance of being a healthier patient.

In an effort to help bring needed information to the public, Pfizer is embarking on a health education campaign. This campaign consists of a series of health information messages which will reach patients through newspapers, magazines and radio. In these messages, patients are informed of the symptoms of diseases such as hypertension and angina and are advised to seek the advice of their physicians in response to these symptoms. Moreover, the messages stress the need for periodic medical examinations to uncover asymptomatic conditions. A sample message in this series appears on the page opposite this letter.

This campaign is one part of a broad new Pfizer communications program. Another aspect of this effort is our Patient Information Program, which consists of providing comprehensive patient information books, such as Learning to Live with Angina, to physicians for distribution to their patients.

I take pride in this program and invite your participation and response.

Sincerely,

Sheldon G. Gilgore

Sheldon G. Gilgore, M.D.
President

...and how Pfizer is helping to make it happen

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A time comes when the job gets tough, as after age 35 or when burdens (like overweight) are added or when vessels that feed the heart muscle lose their ability to bring enough blood to meet oxygen and nutrition needs and remove wastes. Your heart's signal is a condition called angina pectoris.

The symptoms of angina can be any one or more of these:

A sense of tightness or heaviness in your chest
A pain in your shoulder or neck
A sense of fullness, a feeling of "indigestion"

These symptoms are different for different people and at different times in any one person. The important thing is to pay attention, your body is telling you something is wrong. Your heart is giving you a signal to act promptly. See your doctor because angina must and can be treated.

The diagnosis of angina pectoris can be made only by your doctor.

The treatment of angina depends upon a doctor's diagnosis and on the type of angina pectoris you may have. Is it the kind that's caused by spasm? Or thickening of coronary vessels that feed the heart? Or by both?

What's to be done?
Your doctor can help you reduce your cardiac workload by reducing weight, cholesterol, tension and stress. And he has a full range of medications that can relieve coronary spasm, improve the flow of blood to the heart and normalize heart rhythms. You can also help yourself with proper rest and relaxation, time for pleasure and recuperation and a program of moderate exercise.

If your condition is accompanied by elevated blood pressure, your doctor has other medicines that can bring it within normal range. In certain instances, surgery may be called for. Obviously you can't be your own doctor. You need a support system. We call it...

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You are the most important partner.
Only you can spot the warning signs and report them to your physician. And it's you who must decide to accept the guidance and counseling of your physician and pharmacist. When medicines are prescribed, only you can take them as directed.

Your doctor interprets the warning signs, orders your tests, and makes the diagnosis.
Your physician also prescribes the best medication for you among those available—considering each drug's characteristics—and monitors your progress.

All those who discover, develop and distribute medicines complete the partnership.
Pfizer's ongoing research brings you essential medicines for a wide range of diseases, including angina pectoris. Through our development of these and many other medications, we are fulfilling our responsibility as one of your partners in healthcare.

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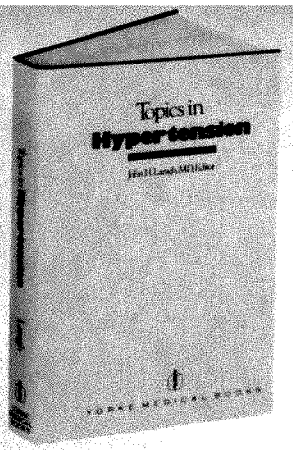

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Please see following page for summary of prescribing information.

K-Lyte/Cl® 50 (Each effervescent tablet in solution supplies 50 mEq potassium and chloride as supplied by potassium bicarbonate and L-lysine monohydrochloride.)
K-Lyte/Cl® (Each effervescent tablet in solution supplies 25 mEq potassium and chloride as supplied by potassium bicarbonate and L-lysine monohydrochloride.)

Description: K-Lyte/Cl 50 and K-Lyte/Cl are oral potassium and chloride supplements. Each K-Lyte/Cl 50 mEq tablet in solution provides 50 mEq of potassium and chloride as supplied by 2.24 gm of potassium chloride, 2.0 gm of potassium bicarbonate, and 3.65 gm of L-lysine monohydrochloride with 1.0 gm of citric acid, saccharin, natural and artificial flavor and artificial color. Each K-Lyte/Cl tablet in solution provides 25 mEq of potassium and chloride as supplied by 1.5 gm of potassium chloride, 0.5 gm of potassium bicarbonate and 0.91 gm of L-lysine monohydrochloride with 0.55 gm of citric acid, saccharin, natural and artificial flavor and artificial color.

Indications and Usage: All K-Lyte® products are used for therapy or prophylaxis of potassium deficiency. They are useful when thiazide diuretics, corticosteroids, or diarrhea cause excessive potassium loss: and when dietary potassium is low. These products may also be useful when potassium therapy is indicated in digitalis intoxication. K-Lyte/Cl 50 and K-Lyte/Cl are recommended in the management of hypokalemia accompanied by metabolic alkalosis and hypochloremia, e.g., as induced by vomiting.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions; chronic renal impairment, metabolic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns or adrenal insufficiency. Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Warnings: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and may be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Precautions: *General precautions* – The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. When interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Therefore, the treatment of potassium depletion requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the ECG, and the clinical status of the patient.
Information for patients – To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, patients should be carefully directed to dissolve each dose completely in the stated amount of water.
Laboratory tests – Frequent clinical evaluation of the patient should include ECG and serum potassium determinations.
Drug interactions – The simultaneous administration of potassium supplements and a potassium-sparing diuretic can produce severe hyperkalemia (see Contraindications). Potassium supplements should be used cautiously in patients who are using salt substitutes because most of the latter contain substantial amounts of potassium. Such concomitant use could result in hyperkalemia.
Usage in pregnancy – Pregnancy Category C – Animal reproduction studies have not been conducted with any of the K-Lyte products. It is also not known whether these products can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. They should be given to a pregnant woman only if clearly needed.
Nursing mothers – Many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from oral potassium supplements, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Usage in children – Safety and effectiveness in children have not been established.

Adverse Reactions: The most common adverse reactions to oral potassium supplements are nausea, vomiting, diarrhea and abdominal discomfort. These side effects occur most frequently when the medication is not taken with food or is not diluted properly or dissolved completely.
Hyperkalemia occurs only rarely in patients with normal renal function receiving potassium supplements orally. Signs and symptoms of hyperkalemia are cardiac arrhythmias, mental confusion, unexplained anxiety, numbness or tingling in hands, feet or lips, shortness of breath or difficult breathing, unusual tiredness or weakness and weakness or heaviness of legs (see Contraindications, Warnings and Overdosage).

Dosage and Administration: *Adults* – One (1) K-Lyte/Cl 50 tablet (50 mEq potassium and chloride) completely dissolved in 6 to 8 ounces of cold or ice water, 1 to 2 times daily, depending on the requirements of the patient. One (1) K-Lyte/Cl tablet (25 mEq potassium and chloride) completely dissolved in 3 to 4 ounces of cold or ice water, 2 to 4 times daily, depending on the requirements of the patient.
Note: It is suggested that all K-Lyte products be taken with meals and sipped slowly over a 5 to 10 minute period.

How Supplied: K-Lyte/Cl® Effervescent Tablets (citrus or fruit punch flavors) are available in cartons of 30, 100 and 250. K-Lyte®/Cl 50 Effervescent Tablets (citrus or fruit punch flavors) are available in cartons of 30 and 100. Each tablet is individually foil wrapped.

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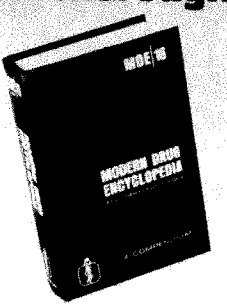

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Effect of Nifedipine on Exercise-Induced Left Ventricular Dysfunction and Myocardial Hypoperfusion in Stable Angina

NADIM M. ZACCA, MD, MARIO S. VERANI, MD, ROBERT A. CHAHINE, MD, and RICHARD R. MILLER, MD

To assess the effects of nifedipine on left ventricular function and regional myocardial perfusion, exercise radionuclide ventriculography was performed in 15 men (median age 59 years) and exercise thallium-201 scintigraphy was done in 11 of them, before and 90 minutes after the oral administration of 20 mg of nifedipine. All patients had stable angina and angiographically proved coronary artery disease without evidence of spasm. Exercise tolerance after administration of nifedipine increased from 343 ± 42 seconds to 471 ± 50 seconds ($p < 0.01$), whereas the peak exercise double product remained essentially unchanged (difference not significant). Ejection fraction improved significantly at rest (from 49 ± 3.6% to 52 ± 3.3%, $p < 0.05$) and at peak exercise (42 ± 3.3% to 47 ± 3.7%, $p < 0.05$). Nifedipine also resulted in an improved segmental wall motion score (4.3 ± 2.3 to 3.0 ± 2.3, $p < 0.05$; 0 = normal and 4 = worst degree of dysfunction). The ejection fraction increased by more than 5% in one third of the patients at rest, and in more than half of the patients at peak exercise. Improved exercise myocardial perfusion occurred in 5 of 11 patients (45%) and in 7 of 28 segments (25%) with reversible hypoperfusion. Thus, nifedipine produces significant improvement in global and regional left ventricular function in patients with coronary artery disease and stable angina. This may be accounted for, at least in part, by improvement in myocardial perfusion.

Nifedipine is a calcium antagonist with potent vasodilating properties.[1–4] It has been used successfully in the treatment of stable angina pectoris and other ischemic syndromes[5–10] and has also been noted to have a negative inotropic effect in the isolated cardiac muscle preparation.[11] However, reports on its effects on myocardial function in patients with cardiac disease have been conflicting.[12–14] In particular, its possible influence on the acute left ventricular dysfunction resulting from stress-induced ischemia has not been sufficiently investigated. The present study was designed to assess the effects of nifedipine on left ventricular function at rest and during exercise in patients with coronary artery disease and stable angina pectoris. Myocardial perfusion scintigraphy was also performed in an attempt to elucidate the mechanism underlying such effects in these patients.

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Material and Methods

Study patients: Fifteen men ranging in age from 47 to 70 years (median 59) were studied. All subjects gave a history of chronic stable angina pectoris and were taking nitrates and beta blocking agents, or both, which were withheld for at least 72 hours before this investigation. No patient had a myocardial infarction within at least 3 months before the trial. No patient had a history of variant angina and S-T segment elevation, or both, during chest pain. Written informed consent was obtained in each case before the administration of nifedipine.

All patients had undergone cardiac catheterization and coronary angiography within the previous 12 months. Critical coronary disease (greater than 70% reduction of luminal diameter) in at least 1 major coronary artery was present in all patients. Ten patients had triple vessel involvement, and 3 had double vessel and 2 single vessel disease (Table I). Neither spontaneous nor catheter-induced spasm was seen during

TABLE I Cardiac Catheterization Data and Results of Supine Bicycle Exercise

Case	Age (yr)	Catheterization Data: RCA (%)	LAD (%)	LCx (%)	LVEDP (mm Hg)	Ex Time (s): Pre-N	Ex Time (s): Post-N	Ex DP × 10^{-3} (mm Hg·beats/min): Pre-N	Ex DP × 10^{-3} (mm Hg·beats/min): Post-N	Max S-T Shift (mm): Pre-N	Max S-T Shift (mm): Post-N
1	53	100	...	...	10	150	210	12.7	13.9	1	1
2	59	100	100	100	10	270	410	24.7	27.5	3	3.5
3	62	100	...	...	12	420	430	22.4	22.6	1	1
4	50	100	75	80	20	415	470	23.1	20.1	1	1
5	70	100*	100	50	10	310	395	12.9	15.1	1.5	0
6	61	95	70	100	17	300	360	24.7	26.0	3	2
7	70	100	100	70	16	265	420	11.5	16.3	1	1
8	60	75	99	100	16	210	480	7.8	14.6	3	2
9	47	80	100	99	10	600	920	20.5	20.7	3	4
10	61	100†	95	100	12	370	630	16.4	16.1	1	0
11	52	...	80	100	8	290	545	20.4	29.0	1	0.5
12	48	100	50	100	9	210	205	12.1	12.4	0.5	0.5
13	66	95	...	100	12	180	270	19.8	15.6	3	2
14	58	80	70		15	750	720	19.9	14.2	0	0
15	58	100	80	100	21	405	600	22.4	24.1	4	5
Mean	...	...	...	...	...	343	471‡	18.1	19.2	1.8	1.5
SEM	...	...	...	...	...	42	50	1.4	1.4	0.3	0.4

* Grafts to RCA, LAD and LCx arteries were all patent. † Graft to LCx artery was patent. ‡ $p < 0.01$ versus pre-N. The percentages refer to the diameter stenosis of the coronary artery.

DP = double product; Ex = exercise; LAD = left anterior descending coronary artery; LCx = Left circumflex coronary artery; LVEDP = left ventricular and diastolic pressure; N = nifedipine; RCA = disease of right coronary artery; SEM = standard error of the mean.

angiography. Because of the severity of the coronary lesions, spasm provocation was not attempted. Cardiac scintigraphic studies were performed in the postabsorptive state according to the following protocol: 1st day, exercise thallium-201 scintigraphy before nifedipine; 2nd day, resting and supine bicycle exercise gated radionuclide ventriculography before and 90 minutes after 20 mg of nifedipine taken orally; and 5th day, exercise thallium-201 scintigraphy 90 minutes after administration of oral nifedipine. The postnifedipine studies were performed 90 minutes after the administration of the drug because human pharmacokinetic investigations have shown that nifedipine reaches a peak concentration in the serum 1 to 2 hours after its oral administration.[15]

A 12 lead electrocardiogram at rest was obtained in each patient before the study. Exercise was performed in the supine position on a calibrated Quinton bicycle ergometer mounted on a radionuclide imaging table. Exercise was initiated at a work load of 200 kg/min and increased by 100 kg/min every 3 minutes. The patients were instructed to pedal at a speed of 50 to 60 rpm. Twelve lead electrocardiograms were recorded at 3 minute intervals just before increasing the work load. Three precordial leads were monitored continuously. Arterial blood pressure was measured with a cuff sphygmomanometer at 1 minute intervals during the study. The patients were exercised to symptomatic end points: moderately severe chest pain, shortness of breath, leg fatigue, or exhaustion. The same exercise protocol was used for the radionuclide angiograms before and after nifedipine. For the perfusion scintigrams, thallium-201 was injected at similar heart rate-blood pressure product before and after administration of nifedipine.

TABLE II Exercise Radionuclide Ventriculography

Case	Ejection Fraction (%): Pre-N Rest	Ejection Fraction (%): Pre-N Ex	Ejection Fraction (%): Post-N Rest	Ejection Fraction (%): Post-N Ex	Wall Motion Score: Pre-N Rest	Wall Motion Score: Pre-N Ex	Wall Motion Score: Post-N Rest	Wall Motion Score: Post-N Ex
1	58	50	56	58	1	3	1	2
2	30	35	34	42	7	7	7	7
3	61	59	64	58	0	2	0	1
4	25	23	28	21	7	7	6	6
5	44	27	47	34	3	5	1	3
6	45	33	56	39	3	4	3	2
7	50	42	57	63	2	4	2	3
8	68	50	68	64	2	6	2	4
9	47	42	48	56	3	6	3	3
10	57	47	62	50	2	5	2	2
11	45	40	50	46	2	2	2	2
12	51	47	50	43	2	3	0	2
13	52	48	59	50	0	2	0	0
14	74	66	69	63	0	0	0	0
15	28	18	31	19	6	8	4	8
Mean	49	42*	52*	47†	2.67	4.27‡	2.20	3.00§
SEM	3.6	3.3	3.3	3.7	2.32	2.28	2.14	2.36

* $p < 0.05$ versus Pre-N Rest. † $p < 0.05$ versus Pre-N Ex and versus Post-N Rest. ‡ $p < 0.01$ versus Pre-N Rest. § $p < 0.05$ versus Post-N Rest and $p < 0.01$ versus Pre-N Ex.

Ex = exercise; N = nifedipine.

The severity of exercise-induced angina was scored as follows: 2+ = moderate or intensity similar to the patient's usual episodes; 3+ = severe or intensity greater than the patient's usual episodes; and 1+ = mild or intensity lesser than usual episodes. A group score before and after administration of nifedipine was obtained by averaging the individual scores. Ischemic S-T shifts on the exercise ECG were considered present when 1 mm or greater horizontal or downsloping S-T segment depression occurred for at least 0.08 second past the J point.

Radionuclide angiography: An in vivo red blood cell labeling technique was used.[16] For this purpose, 7.5 mg of stannous pyrophosphate (Pyrolite, New England Nuclear, North Billerica, Massachusetts) was injected intravenously, followed 30 minutes later by 20 mCi of technetium-99m pertechnetate. Imaging was performed at rest in the anterior projection and in the left anterior oblique (LAO) projection, which allowed best delineation of the interventricular septum (usually 40 to 45° LAO). Exercise studies were performed only in the LAO projection. An all-purpose parallel hole collimator was utilized. Images were collected and processed using a gamma scintillation camera interfaced with an on-line dedicated computer (Ohio Nuclear 420-550 system). Multigated equilibrium blood pool imaging was performed during a preset time for 3 minutes at rest and for each work load. The cardiac cycle was divided into 16 frames allowing a minimum of 200,000 counts/frame to be obtained. The left ventricular ejection fraction was calculated using a computer program following Burow's technique.[17] A normal ejection fraction response to exercise is defined as a 5% increase from rest to peak exercise and an absolute value equal to or greater than 50%.[17]

Left ventricular wall motion was assessed qualitatively and independently by 3 experienced observers as described previously.[18] Briefly, the ventricle was divided into anterolateral, apical, and inferior walls on the anterior view; and septal, inferoapical, and posterolateral walls on the LAO view. Regional wall motion was assessed using a 5 point score system: 0 = normal, 1 = mild hypokinesia, 2 = moderate hypokinesia, 3 = severe hypokinesia, and 4 = akinesia or dyskinesia. A regional wall motion index was thus obtained by averaging the individual scores of all observers for each patient.

Exercise thallium-201 imaging: Eleven patients were evaluated with exercise thallium-201 scintigrams before and after nifedipine. The exercise protocol was similar to the radionuclide angiography protocol. Approximately 60 seconds before the termination of exercise, 1.5 mCi of thallium-201 was injected intravenously. Immediately after the completion of exercise and 4 hours later, imaging was performed with the patient supine in the anterior, 45°, and 70° LAO projections, using the same imaging system (Ohio Nuclear 420-550 system). A total of 400,000 counts were collected for each image.

Scintigrams were divided into 5 segments for analysis as follows: anterior, inferior, septal, apical, and posterolateral. Two techniques of interpretation were used. The first (a point score technique) consisted of independent visual interpretation of computer-processed scintigrams (after contrast enhancement and 20% background subtraction). The peak exercise and delayed images were compared side by side, before and after nifedipine administration. Perfusion defects were graded as follows: 0 = no defect; +1 = mild decrease in thallium-201 uptake; +2 = moderate decrease in thallium-201 uptake; +3 = greatly reduced or absent thallium uptake. The 2nd scintigraphic method used for analysis was a semiquantitative count-ratio technique. A ratio was determined from the counts in each segment over a normal area of myocardium

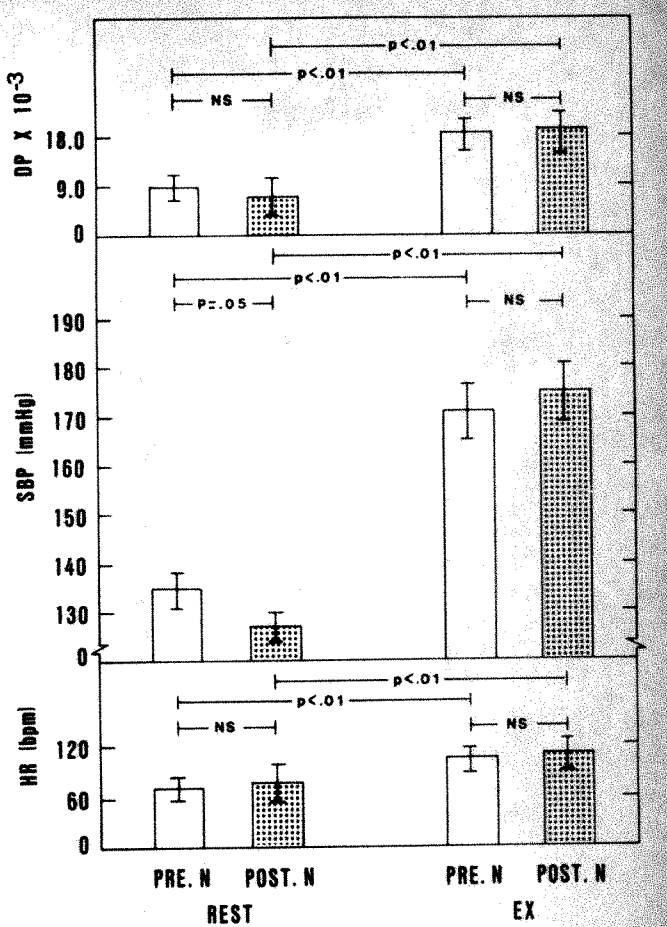

FIGURE 1. Effect of nifedipine on resting and exercise variables. bpm = beats/min; DP = double product (systolic blood pressure X heart rate); EX = exercise; HR = heart rate; N = nifedipine; Pre. N = before administration of nifedipine; Post. N = after administration of nifedipine; SBP = systolic blood pressure (mm Hg).

defined as the zone, in each separate projection, with the highest count density. The regions of interest in the abnormal segments were selected as representative of a portion of the most abnormal perfusion. Assuming that the areas of maximal perfusion in each projection represented normal perfusion, the derived ratio between the two segments multiplied by 100 corresponds to the percent of normal uptake in the abnormally perfused segment. For example, a ratio of 1 would be expected to represent a normal value with homogeneous perfusion. A ratio of less than 80% was considered abnormal.[19] A perfusion defect was considered changed if the compared count ratio varied by 20% or more. Changes in regional perfusion were considered present only if confirmed by both methods of analysis.

Statistical analysis: Data are expressed as mean ± standard error of the mean (SEM). The Wilcoxon test was used as a multiple range test for the comparison of individual pairs of groups. P values of 0.05 or less were considered significant.

Results

Resting Data

Blood pressure, heart rate, and double product: At rest, the heart rate was unchanged (p = NS) after nifedipine (66 ± 3 versus 69 ± 3 beats/min). The supine

systolic blood pressure decreased from 135 ± 4 to 127 ± 3 mm Hg (p = 0.05). The double product was unchanged (9.0 ± 0.6 × 10^3 versus 8.8 ± 0.4 × 10^3) (Fig. 1).

Radionuclide ventriculography: ejection fraction: Eight patients had a normal resting left ventricular ejection fraction (that is, 50% or greater) before nifedipine. Nifedipine slightly but significantly improved the ejection fraction at rest (49 ± 3.6% before nifedipine to 52 ± 3.3% after nifedipine, p <0.05). In 5 patients (33%), it did so by 5% or greater, thereby normalizing the ejection fraction in 2 of them (Table II).

Segmental wall motion abnormalities: Twelve patients had wall motion abnormalities at rest before nifedipine was administered. Four patients had improvement in their wall motion abnormalities at rest after nifedipine was given. No patient had worsening of wall motion. The mean wall motion index at rest was slightly improved after nifedipine, but the difference failed to attain statistical significance (2.2 ± 2.14 versus 2.67 ± 2.32, p >0.05) (Table II).

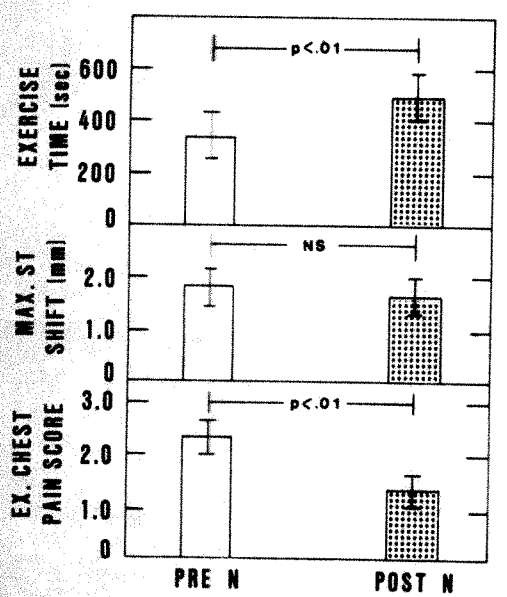

FIGURE 2. Effect of nifedipine on exercise performance. EX. = exercise; MAX. = maximal. Other abbreviations as in Figure 1.

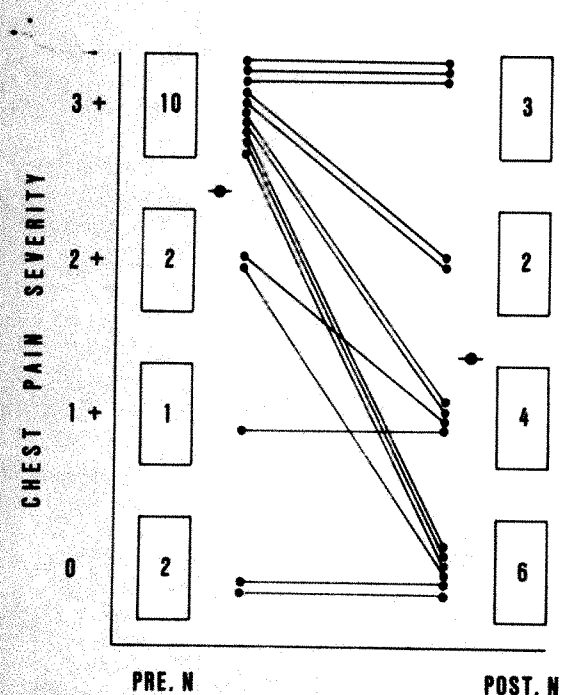

FIGURE 3. Effect of nifedipine on the severity of chest pain at peak exercise in individual patients. 0 = no angina, 1+ = mild angina (subjectively less than the patient's usual severity of chest pain); 2+ = moderate chest pain (usual anginal severity); 3+ = severe chest pain (more than usual severity). The total number of patients in each angina class is shown inside the rectangles.

Exercise Data

Blood pressure, heart rate, and double product: At peak exercise, there was no difference (p >0.05) before and after administration of nifedipine in heart rate (104 ± 6 versus 109 ± 6 beats/min), systolic blood pressure (171 ± 6 versus 174 ± 6 mm Hg) and double product (18.1 ± 1.4 × 10^3 versus 19.2 ± 1.4 × 10^3 mm Hg beats/min) (Fig. 1). In 3 patients, the peak exercise double product decreased after nifedipine was administered in association with an unchanged (2 patients) or increased (1 patient) exercise tolerance. In 2 other patients, the exercise double product remained unchanged after administration of nifedipine despite an improvement in exercise performance (Table I).

Exercise time: The exercise time (Fig. 2) before the oral administration of nifedipine was 343 ± 42 seconds and increased to 471 ± 50 seconds after administration of nifedipine (p <0.01). Exercise tolerance increased in all but 3 patients.

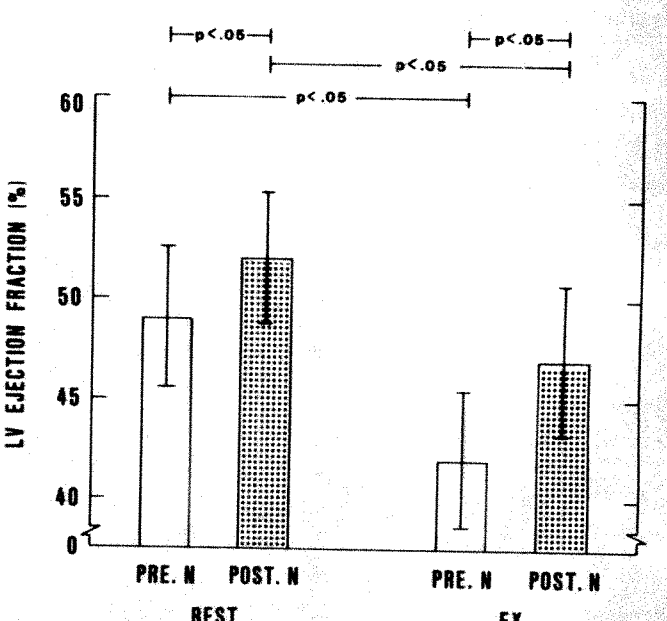

FIGURE 4. Effect of nifedipine on the rest and exercise left ventricular ejection fraction. LV = left ventricular. Other abbreviations as in Figure 1.

Severity of angina: Ten patients (67%) had moderately severe chest pain (3+) at peak exercise before nifedipine, 2 patients (13%) had angina of 2+ severity, 1 patient (7%) had mild angina (1+), and 2 patients (13%) had no chest pain at peak exercise before administration of nifedipine. The severity of chest pain during bicycle exercise was less in 9 (69%) of 13 patients after nifedipine. Four (31%) of the 13 patients became angina-free at peak exercise. No patient had worsening of angina after nifedipine (Fig. 3). The peak exercise chest pain score was less after nifedipine (2.3 ± 0.3 before versus 1.1 ± 0.3 after nifedipine, $p < 0.01$) (Fig. 2).

S-T segment shift: The mean maximal S-T segment shift during exercise (Fig. 2) was 1.8 ± 0.3 mm before and 1.6 ± 0.4 mm after nifedipine (p = NS). Ischemic S-T shifts were present during exercise in 13 patients before nifedipine and in 10 patients after nifedipine. However, in 8 patients, maximal S-T segment shifts improved (greater than 1 mm) (4 patients) or remained unchanged (4 patients) after nifedipine despite an increase in work load.

Ejection fraction: Before the administration of nifedipine there was a significant decline in left ventricular ejection fraction from resting to peak exercise (49 ± 3.6% to 42 ± 3.3%, $p < 0.05$) (Fig. 4). Although a significant decrease in ejection fraction from rest to exercise continued to occur after nifedipine (52 ± 3.3% at rest to 47 ± 3.7% at peak exercise, $p < 0.05$), the peak exercise ejection fraction was higher after nifedipine (47 ± 3.7% after versus 42% ± before nifedipine, $p < 0.05$), with greater than 5% improvement in exercise ejection fraction in 8 patients.

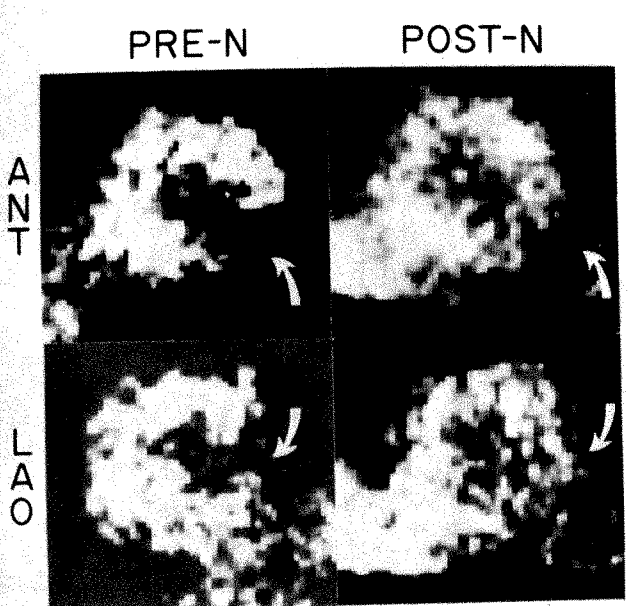

FIGURE 5. Thallium-201 scintigrams taken in the anterior (ANT) and 45° left anterior oblique (LAO) projections immediately after exercise. The 2 scintigrams on the **left** are the exercise studies before administration of nifedipine (PRE-N) and show large perfusion defects in the apical and posterolateral regions of the left ventricle. Five days later, 90 minutes after the oral administration of 20 mg of nifedipine (POST-N) (exercise scintigrams on the **right**), perfusion is markedly improved in the aforementioned regions.

TABLE III Results of Exercise Thallium-201 Scintigraphy in 11 Patients

Case	Peak Ex Results of Thallium-201		
	Point Score		Count/Ratio Changes
	Pre-N	Post-N	
2	9	9	NC
5	9	9	NC
7	6	6	NC
8	6	2	Improved
9	6	4	NC
10	3	3	Improved
11	5	2	Improved
12	2	1	Improved
13	1	1	NC
14	2	2	NC
15	8	7	Improved

Ex = exercise; N = nifedipine; NC = no change; Improved = greater than 20% change.

Wall motion abnormalities: Eleven patients (73%) had deterioration in wall motion with exercise before nifedipine, 3 had no further changes, and 1 remained normal. In contrast, only 7 patients (47%) had deterioration of wall motion with exercise after nifedipine, 5 had no further changes, 2 remained normal, and 1 had improvement. After nifedipine was administered, the exercise wall motion index was also significantly higher than the rest wall motion index (3.0 ± 2.4 versus 2.2 ± 2.1, $p < 0.05$). However, the peak exercise wall motion index was improved after versus before administration of nifedipine (3.0 ± 2.4 versus 4.3 ± 2.3, $p < 0.01$) (Table II).

Exercise Thallium-201 Scintigraphy

All patients showed perfusion abnormalities with exercise before nifedipine was given. Five (45%) of 11 patients had definite improvement of the exercise perfusion defect after nifedipine (Table III).

Of 22 exercise perfusion defects in 11 patients before administration of nifedipine noted by the point score technique, 7 (32%) showed improvement at peak exercise after nifedipine. When the count-ratio technique was used for comparison, 28 defects were noted in the 11 patients. Of these, 7 (25%) had improvement of more than 20% (Fig. 5).

Discussion

This investigation provides objective evidence that nifedipine improves left ventricular performance in patients with coronary artery disease and stable angina pectoris. The drug had a similar beneficial effect on resting and exercise ejection fraction. Furthermore, the exercise-induced regional wall motion abnormalities were less marked after nifedipine. In certain patients, nifedipine appeared to improve the exercise-induced myocardial perfusion defects. In addition, this study confirms the previous observation that nifedipine prolongs exercise duration and decreases ischemia at peak exercise.[7,9,10]

The improved exercise time in these patients was statistically significant and could not be ascribed to a training effect because all patients had undergone several exercise tests previously. Exercise tolerance improved by 37% after nifedipine in the group as a whole. This improvement is within the range (23 to 64%) previously described.[20–23] In addition to the prolongation of exercise time, there was evidence of a reduction in the severity of ischemia as indicated by the lesser severity of angina and the magnitude of S-T segment depression.[24,8] Angina at peak exercise was less severe in 69% of the patients studied, and in 31% of those exercise-induced angina was abolished. In Prempree's series,[23] 4 of 6 patients with stable angina were pain-free at peak exercise on the treadmill despite significantly higher heart rates. The European double-blind or long-term open trials of nifedipine,[20] as well as preliminary results from American studies,[9,10] have demonstrated a significant reduction in the average number of anginal attacks and in the consumption of nitroglycerin in the patients receiving nifedipine compared with results from placebo. Ischemic S-T segment depression was still present in most patients at peak exercise after administration of nifedipine; however, in 53% of the cases the S-T segment shift after administration of nifedipine either improved (greater than 1 mm) or remained unchanged while the work load increased.

Due to its arterial dilating effect, nifedipine decreases systemic vascular resistance and thus the left ventricular afterload while having little effect on preload.[20,30–32] Consequently, the heart rate may increase by reflex mechanism.[33,34] In our group of patients, the resting systolic blood pressure decreased after nifedipine. The peak exercise double product either decreased or remained unchanged despite an increase in exercise duration after nifedipine, suggesting that 1 mechanism by which nifedipine reduced exercise-induced angina and improved performance in those patients was by reducing the double product and thereby myocardial oxygen demand at a given exercise load. Thus, the improvement in exercise-related angina is at least partly due to peripheral effects of nifedipine.

The question regarding the net effect of nifedipine on ventricular function in the presence of critical coronary artery disease has not been sufficiently addressed previously. Contrary to former concern,[11] nifedipine did not appear to have a deleterious effect on left ventricular function. Our investigation demonstrates a significant improvement in the resting as well as the exercise ejection fraction after the administration of nifedipine. The ejection fraction improved by more than 5% in one third of the patients at rest, and in more than half of the patients at peak exercise. Importantly, there was no significant deterioration (ejection fraction decrease by 5% or more) in any patient. In contrast, there was a dramatic normalization of the left ventricular ejection fraction response to exercise after nifedipine was administered to 2 patients (Patients 7 and 9). This clearly suggests that whatever negative inotropic action nifedipine may have does not result in a clinically important effect despite severe left ventricular dysfunction (Patients 2, 4, and 15). The direct negative inotropic effect is probably offset by its arterial dilator effect bringing about a change in baroreceptor tone that results in an increase in heart rate and a secondary increase in contractility. The lack of deleterious effect on myocardial function is also supported by the absence of worsening wall motion at rest or peak exercise after administration of nifedipine. The peak exercise wall motion index was improved after nifedipine, and only 47% of patients had deterioration in wall motion after nifedipine from rest to exercise, compared with 73% before nifedipine.

Can the beneficial effects of nifedipine be fully accounted for by the peripheral and reflex mechanisms? Lichtlen et al.[35,36] demonstrated that nifedipine increased poststenotic perfusion of ischemic areas induced by exercise or rapid atrial pacing. In our study, exercise thallium-201 perfusion scintigraphy was performed in 11 patients and improvement in thallium uptake was noted in 5 (45%). It is therefore suggested that in those patients the distribution of myocardial blood flow may have been improved with nifedipine.

In summary, nifedipine is demonstrated to have a beneficial effect on resting and exercise left ventricular function in patients with coronary artery disease and chronic stable angina. This effect appears to be multifactorial and involves peripheral mechanisms in addition to possible improvement in myocardial perfusion.

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Randomized Double-Blind Comparison of Verapamil and Nifedipine in Chronic Stable Angina

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A randomized double-blind crossover trial was performed in 32 patients with chronic stable angina to compare the antianginal actions of verapamil (120 mg 3 times daily) and nifedipine (20 mg 3 times daily). Efficacy was assessed using objective end points obtained by computer-assisted exercise testing and 24 hour ambulatory monitoring for S-T segment shift. Twenty-eight patients completed the trial. The mean exercise time to produce angina improved from 5.7 ± 0.3 minutes (mean ± standard error of the mean) in patients on placebo, to 7.9 ± 0.5 minutes in those on nifedipine and 10.0 ± 0.7 minutes in those on verapamil. Similar improvement was seen in all other objective variables. Generally, verapamil produced mild bradycardia and nifedipine mild tachycardia. Four patients complained of palpitations and angina after ingestion of nifedipine and were identified by ambulatory monitoring to have tachycardia and persistent S-T depression. These opposite effects on heart rate may explain the differences in efficacy between these 2 potent calcium ion antagonists.

The emphasis on drug treatment of angina pectoris has shifted from nitrates to beta-adrenoceptor blocking agents in the last 20 years, and now there is great interest in calcium channel blocking drugs as an additional therapeutic measure in chronic stable angina. This interest is mainly attributable to the work of Maseri, who clearly demonstrated that coronary arterial spasm plays an important part in the genesis of angina[1] and that this spasm is antagonized by the slow calcium channel blocking drugs.[2] There are now 12 drugs that are claimed to have the property of slow calcium channel blockade, but it is not known which are likely to become first line agents in the treatment of angina pectoris.[3]

The 2 most widely used drugs in this group are verapamil and nifedipine. Verapamil was first introduced in 1962 as a coronary vasodilator and was later demonstrated to be a powerful antiarrhythmic agent because of its depressor action on the atrioventricular node.[4] Nifedipine was developed as a specific calcium channel blocking drug and has been shown to be a powerful antianginal agent in vasospastic angina.[5–7] It has also been used in patients with chronic stable angina with variable results.[3,8] Direct comparisons of these 2 drugs in chronic stable angina are considered essential, and we have conducted a randomized double-blind placebo-controlled crossover trial comparing their actions in a large group of patients with chronic stable angina.

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Material and Methods

Thirty-two patients (30 men and 2 women aged 40 to 69 years) with chronic stable exertional angina were recruited for the study.

Inclusion criteria: The patients were required to have unequivocal evidence of obstructive coronary artery disease, to have symptomatic stable angina, and to have S-T segment depression and angina on maximal treadmill exercise testing. Coronary artery disease was confirmed by selective coronary arteriography in 21 patients or by transmural myocardial infarction in the 12 months preceding the trial in 11 patients. All had classic angina on exertion relieved by rest and sublingual administration of glyceryl trinitrate with a minimal incidence of 4 attacks/week. All had classic anginal pain on treadmill exercise testing with at least 1 mm S-T segment depression with a slope less than 0.1 V/s in 2 bipolar leads (CM5 and CC5) during exercise. Only patients physically capable and mentally motivated for repeated treadmill exercise were entered into the final trial.

Exclusion criteria: All patients more than 70 years of age and women in the child-bearing age were excluded. Myocardial infarction in the preceding 4 months, unstable angina and severe symptoms that were clinically judged as unsuitable for placebo treatment, overt cardiac failure, resting blood pressure levels in excess of 160/100 mm Hg, and insulin-dependent diabetes mellitus were other exclusion criteria. All patients receiving diuretic drugs, digitalis, and other cardiovascular drugs were excluded, as were patients showing more than 0.5 mm S-T depression on standing, hyperventilation, and the Valsalva maneuver. Patients who did not have classic angina on the initial diagnostic treadmill exercise test with 1 mm S-T segment depression in both bipolar leads were also excluded.

Trial design: All patients underwent a diagnostic exercise test performed without any treatment (26 patients) or 4 weeks after complete withdrawal of long-term medical therapy. Two were taking long-acting nitrates and 4 were taking propranolol (40 mg 3 times daily) before inclusion in the trial. None were given any other cardiac drugs except the trial drugs and sublingual nitrates during the trial period. Sublingual nitrates were only allowed for relief of an anginal episode when it occurred, and patients were clearly and repeatedly instructed not to use them prophylactically and to maintain a diary of their glyceryl trinitrate consumption.

The drugs were administered using a double-dummy technique. During the first 2 weeks (which comprised the placebo run-in phase) the patients took 3 tablets, 1 of verapamil and 2 of nifedipine placebo, 3 times daily. In the crossover phase the 3 tablets were either active verapamil and placebo nifedipine, or active nifedipine and placebo verapamil. This phase was double-blind. All verapamil tablets including placebo were identical in appearance, and all nifedipine capsules including both doses and placebo were identical. The tablets were packed in plastic containers with compartments identifying the day of the week and the time of drug administration.

TABLE I Treadmill Protocol

Stage	Time (min)	Speed (miles/h)	Gradient (%)
1	3	2	0
2	3	3	4
3	3	3	8
4	3	3	12
5	3	3	16
6	3	3	20
7	3	4.5	20

The trial design was a double-blind crossover study of 4 weeks in each treatment period after the 2 weeks placebo run-in period. The dosage schedules were nifedipine 20 mg 3 times daily or verapamil 120 mg 3 times daily, and the randomization was based on a table of random numbers. The active drugs were crossed over at the end of each 4 week period with a 1 week washout period in between.

Formal exercise testing was repeated at the end of the placebo, and each 4 week period of active drug therapy. Twenty-four hour ambulatory monitoring (Oxford Medilog II) and estimation of left ventricular function by systolic time intervals (analyzed by an on-line computer system) were also performed at the end of each period to establish changes in resting heart rate, left ventricular function, and the appearance of conduction defects.

Exercise testing: All tests were performed using a motor-driven treadmill, the speed and gradient of which were regularly calibrated, and the program (Table I) was governed by a computer (Marquette Computer Assisted System for Exercise). Two bipolar leads (CM5 and CC5) were continuously recorded before, during and after exercise in a 25:1 compressed format. Digital printouts of S-T depression at the J point, S-T slope, heart rate, and ectopic count were generated for every minute of the test and for a final analog trend

TABLE II Exercise Test Data on Nifedipine and Verapamil Therapy

	Placebo Period	Nifedipine (20 mg 3 times daily)	Verapamil (120 mg 3 times daily)
Exercise time (min)	5.7 ± 0.3	7.9 ± 0.5	10.0 ± 0.7
Work load (units)	5.6 ± 0.4	13.6 ± 0.9	23.8 ± 1.2
Resting heart rate (beats/min)	74 ± 2	77 ± 2	68 ± 2
Maximal heart rate (beats/min)	125 ± 3	130 ± 3	124 ± 3
Heart rate gain (beats/min)	51 ± 3	53 ± 3	56 ± 2
Heart rate recovery 5 min (beats/min)	53 ± 4	46 ± 2	50 ± 2
Double product (peak)	154 ± 8	159 ± 8	164 ± 6
1 mm time CM5 (min)	3.9 ± 0.3	5.8 ± 0.4	7.1 ± 0.5
1 mm time CC5 (min)	3.9 ± 0.3	6.0 ± 0.4	7.4 ± 0.6
2 mm time CM5 (min)	5.3 ± 0.4	7.5 ± 0.4	9.5 ± 0.7
2 mm time CC5 (min)	5.1 ± 0.3	7.7 ± 0.4	9.5 ± 0.6
MS-T CM5 (mm)	2.0 ± 0.2	2.9 ± 0.2	1.8 ± 0.2
MS-T CC5 (mm)	1.9 ± 0.2	1.9 ± 0.2	1.7 ± 0.2
MS-T/ex. time CM5 (mm)	0.386 ± 0.036	0.256 ± 0.027	0.181 ± 0.019
MS-T/ex. time CC5 (mm)	0.361 ± 0.03	0.242 ± 0.020	0.172 ± 0.016
MS-T/METS CM5 (mm)	0.13 ± 0.014	0.065 ± 0.007	0.049 ± 0.005
MS-T/METS CC5 (mm)	0.12 ± 0.010	0.062 ± 0.006	0.037 ± 0.003
MS-T/O_2 consumption CM5 (mm)	0.036 ± 0.004	0.018 ± 0.002	0.012 ± 0.001
MS-T/O_2 consumption CC5 (mm)	0.033 ± 0.003	0.018 ± 0.002	0.011 ± 0.001
S-T (same ex. time) CM5 (mm)	1.8 ± 0.2	1.0 ± 0.2	0.7 ± 0.2
S-T (same ex. time) CC5 (mm)	1.7 ± 0.2	1.0 ± 0.1	0.6 ± 0.2
Heart rate (same ex. time) (beats/min)	122 ± 3	117 ± 3	106 ± 3
S-T recovery in 5 min CM5 (mm)	1.8 ± 0.2	1.5 ± 0.2	1.4 ± 0.1
S-T recovery in 5 min CC5 (mm)	1.7 ± 0.1	1.6 ± 0.1	1.4 ± 0.1

All values are mean ± standard error of the mean.
Ex. time = exercise time; METS = metabolic equivalents; MS-T = maximal S-T depression; O_2 = oxygen.

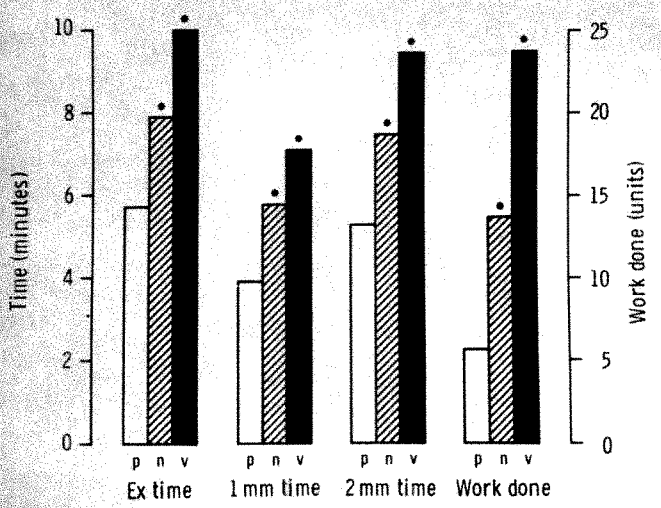

FIGURE 1. Comparison of exercise time (Ex time), time to 1 and 2 mm S-T segment depression, and work done on placebo, nifedipine, and verapamil therapy. n = nifedipine (20 mg 3 times daily); p = placebo; v = verapamil (120 mg 3 times daily); **asterisk** indicates $p < 0.001$ compared with placebo. For standard errors, see Table II.

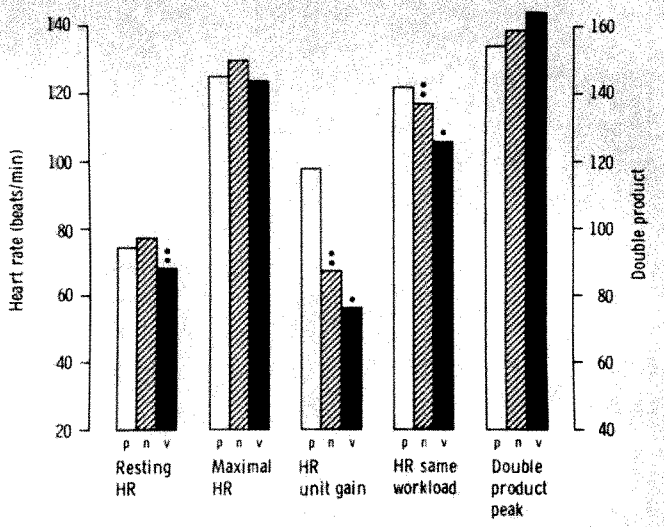

FIGURE 3. Changes in heart rate variables on placebo, nifedipine, and verapamil therapy. Note the mild resting tachycardia (p not significant) produced by nifedipine and the bradycardia by verapamil. Both drugs reduce heart rate unit gain and heart rate at the same work load as placebo, but verapamil has a more significant bradycardiac effect. Neither drug affects the double product at peak exercise. HR unit gain = heart rate gain divided by exercise time. Abbreviations as in Figure 1.

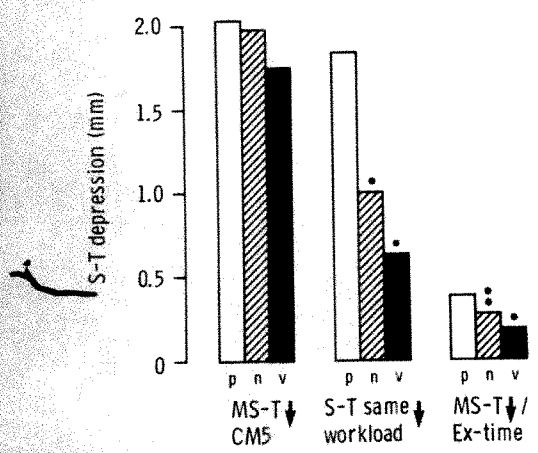

FIGURE 2. Exercise-induced S-T segment changes in bipolar lead CM5 during placebo, nifedipine, and verapamil therapy. **Double asterisks** indicate $p < 0.01$; MS-T = maximal S-T depression. Other abbreviations as in Figure 1.

plot of each complete test. Systolic blood pressure was measured every 3 minutes and at termination of exercise with a mercury-in-glass sphygmomanometer.

The following variables were calculated from the computer printouts[9]:

Time variables were as follows: (1) exercise time required in minutes for production of angina or termination of exercise, (2) work load = distance walked in kilometers multiplied by the sine of the angle of the treadmill in degrees, (3) 1 mm time/2 mm time = time required to produce 1 and 2 mm S-T segment displacement for both bipolar leads CM5 and CC5.

S-T segment variables (for 2 bipolar leads): (1) S-T segment displacement at peak exercise (MS-T), (2) MS-T divided by exercise time, (3) MS-T divided by predicted oxygen consumption, (4) MS-T divided by predicted metabolic equivalents (METS), (5) S-T segment recovery in 5 minutes after exercise, and (6) S-T segment depression at the same exercise time on drug therapy as during placebo.

Heart rate variables were as follows: (1) resting heart rate, (2) maximal heart rate, (3) heart rate gain = maximal heart rate minus resting heart rate, (4) heart rate unit gain = heart rate gain divided by exercise time, (5) heart rate at the same exercise time on drug therapy as during placebo, (6) heart rate recovery in 5 minutes after exercise, and (7) double product = the product of systolic blood pressure and heart rate divided by 100.

All exercise tests were maximal or limited by angina, dyspnea, fatigue, or pain in the legs. All were performed in the morning 90 to 150 minutes after the last dose and after 30 minutes rest in a temperature-controlled laboratory. The standard safety precautions as recommended by the American Heart Association were followed.[10]

Ambulatory monitoring: Continuous ambulatory monitoring of the same 2 leads of the electrocardiogram (CM5 and CC5) was performed using a frequency-modulated tape recorder with a quartz-controlled time channel (Oxford Medilog Mark II) for a minimum of 24 hours. All tapes were analyzed visually for prolongation of the P-R interval or higher degrees of heart block. Mean hourly heart rates were obtained using a computer program. The tapes were then played into a minicomputer that stored minute-averaged values of mean, minimal, and maximal heart rate and S-T segment values for 24 hours on a 5.1/4 inch floppy disc. Software analysis enabled acquisition of objective variables such as maximal S-T depression, episodes of S-T depression over 1 mm in 24 hours, and the number of minutes in which the heart rate exceeded a preset figure (100 beats/min).[11]

Left ventricular function: This function was estimated noninvasively by measuring systolic time intervals with the patient in the supine posture. The first derivative of the electrical impedance cardiogram (dZ/dt) was used as the central arterial pulse wave form. The impedance cardiogram and electrocardiogram were simultaneously fed into a purpose built minicomputer that calculated the preejection period, the left ventricular ejection time, the ratio between left ventricular

TABLE III Probability Values for Placebo, Nifedipine, and Verapamil Therapy

	Placebo Versus Nifedipine	Placebo Versus Verapamil	Nifedipine Versus Verapamil
Exercise time (min)	<0.001	<0.001	<0.001
Work load (units)	<0.001	<0.001	<0.001
Resting heart rate (beats/min)	NS	<0.01	<0.001
Maximal heart rate (beats/min)	<0.05	NS	<0.01
Heart rate gain (beats/min)	NS	NS	NS
Heart rate recovery 5 min (beats/min)	<0.01	NS	<0.05
Double product (peak)	NS	NS	NS
1 mm time CM5 (min)	<0.001	<0.001	<0.01
1 mm time CC5 (min)	<0.001	<0.001	<0.001
2 mm time CM5 (min)	<0.001	<0.001	<0.001
2 mm time CC5 (min)	<0.001	<0.001	<0.001
MS-T CM5 (mm)	NS	NS	NS
MS-T CC5 (mm)	NS	NS	NS
MS-T/ex. time CM5 (mm)	<0.01	<0.001	<0.01
MS-T/ex. time CC5 (mm)	<0.001	<0.001	<0.01
MS-T/METS CM5 (mm)	<0.001	<0.001	<0.001
MS-T/METS CC5 (mm)	<0.001	<0.001	<0.001
MS-T/O_2 consumption CM5 (mm)	<0.001	<0.001	<0.01
MS-T/O_2 consumption CC5 (mm)	<0.001	<0.001	<0.001
S-T (same ex. time) CM5 (mm)	<0.001	<0.001	<0.05
S-T (same ex. time) CC5 (mm)	<0.001	<0.001	<0.01
Heart rate same ex. time (beats/min)	<0.05	<0.001	<0.001
S-T recovery in 5 min CM5 (mm)	<0.05	<0.01	NS
S-T recovery in 5 min CC5 (mm)	NS	NS	NS

NS = not significant. Other abbreviations as in Table II.

ejection time and preejection period (PEP/LVET ratio), the interval between the peak of the R wave of the electrocardiogram and impedance cardiogram (RZ interval), and the ratio between the amplitude of the impedance wave form and the RZ interval (dZ/dt/RZ ratio).[12] The last 2 variables bear a close correlation to the other systolic time intervals and have been used for serial estimation of left ventricular function.[12–16] Stroke volume and cardiac output were also estimated from the impedance cardiogram.[17]

In this study, we used 100 beat averaging during quiet supine rest with additional averaging of the first 20 beats recorded with breath held in expiration. All studies were performed in the morning after supine rest for 20 minutes.

Statistical analysis of all data was performed with a programmed calculator using Student's paired t test (2 tailed).

Clinical interviews were conducted regularly to detect adverse side effects, which were noted on a standard questionnaire. The project was approved by the Hospital Ethical Committee and informed consent was obtained from all patients.

Results

Thirty-two patients (30 men and 2 women) were entered into the study. Twenty-eight patients completed all phases of the study and all data concern these patients.

Placebo (Fig. 1 to 3, Tables II to IV): All patients discontinued exercise because of angina. The exercise time required to produce angina ranged from 3.3 to 9.9 minutes (mean ± standard error of the mean 5.7 ± 0.3 minutes). The mean resting heart rate was 74 ± 2 beats/min and this increased to a mean maximum of 125 ± 3 beats/min at 5.7 minutes of exercise. The heart rate gain was 51 beats/min and the heart rate increase per minute of exercise was 9.1 beats/min. The peak double product was 154 ± 8 units. The heart rate recovery 5 minutes after exercise was 53 ± 4.2 beats/min. The maximal S-T segment depression in lead CM5 ranged between 1.0 and 4.3 mm, the mean being 2.0 ± 0.2 mm. The mean exercise time required to produce 1 and 2 mm S-T depression was 3.9 ± 0.3 and 5.3 ± 0.4 minutes, respectively. The S-T segment recovered by 1.8 ± 0.2 mm at 5 minutes after exercise. Lead CC5 showed similar values. Twenty-four hour ambulatory Holter monitoring revealed a range of 7 to 29 episodes of S-T depression over 1 mm in 24 hours with a mean of 15 ± 2 episodes. The maximal depth of S-T depression varied from 1.3 to 4.2 mm with a mean of 2.3 ± 0.2 mm. The glyceryl trinitrate consumption was 11.1 ± 2.0 tablets/week.

Verapamil (Fig. 1 to 3): Of the 28 patients who completed the study, 11 became angina-free on treadmill exercise after 4 weeks of treatment. The exercise time ranged from 3.8 to 18.5 minutes (mean 10.0 ± 0.7). This was significantly greater than the mean placebo exercise time ($p < 0.001$). The mean resting heart rate was 68 ± 2 beats/min and the maximal exercise heart rate was unaltered at 124 ± 3 beats/min. The heart rate gain in 10.0 minutes of exercise was 56 beats/min, giving a heart rate increase per minute of exercise of 5.6 beats/min. The heart rate at the same exercise time as placebo was 106 ± 3 beats/min ($p < 0.001$). Heart rate recovery was unaltered at 50 ± 2 beats/min. The standing systolic blood pressure at rest of 110 ± 7 mm Hg during placebo was not significantly altered by treatment with verapamil. The peak exercise systolic blood pressure was 123 ± 7 mm Hg during placebo, and a mild increase to 130 ± 9 mm Hg (p = NS) was observed during therapy with verapamil. The peak double

TABLE IV Holter Monitoring Data on Nifedipine and Verapamil Therapy

Variable	Placebo	Nifedipine	Verapamil	p Value*
Episodes of S-T depression over 1 mm in 24 hours	15 ± 2	15 ± 2 (p = NS)	9 ± 2 (p <0.01)	<0.01
Maximal depth of S-T depression in 24 hours	2.3 ± 0.2	2.1 ± 0.2 (p = NS)	1.7 ± 0.2 (p <0.05)	NS
Minutes (n) in which HR exceeded 100 beats/min in 24 hours	42 ± 5	101 ± 10 (p <0.01)	4 ± 1 (p <0.01)	<0.001
Patients (n) in whom variable 3 exceeded placebo values	. . .	20	1	. . .

* Probability value between verapamil and nifedipine. The p values in parentheses represent the comparison with placebo and the active drug.
HR = heart rate.

product was 164 ± 6 units, but the double product at the same exercise time as placebo was reduced to 122 ± 5 units (p <0.001). The maximal S-T segment depression in lead CM5 ranged from 0.1 to 2.9 mm, the mean value being 1.8 ± 0.2 mm. This S-T depression now occurred at 10.0 minutes instead of 5.7 minutes on placebo, and all the corrected S-T segment variables showed significant improvement. The time required to produce 1 and 2 mm of S-T depression increased to 7.1 ± 0.5 and 9.5 ± 0.7 minutes (p <0.001). The S-T segment values at the same exercise time as placebo decreased from 1.8 ± 0.2 mm to 0.7 ± 0.2 mm (p <0.001). The S-T segment recovery 5 minutes after exercise was 1.4 ± 0.1 mm, and the ratio of peak S-T to S-T recovery was 78%. The S-T segment changes in lead CC5 were similar to those in CM5.

The ambulatory monitoring tapes were analyzed in detail for heart rate and S-T segment changes. The mean hourly heart rates are shown in Figure 4. Verapamil produced a slowing of the heart rate during the entire 24 hours compared with placebo. The mean number of minutes during which the heart rate exceeded 100 beats/min was 42 ± 5 during placebo, and this was reduced to 4 ± 0.2 during verapamil treatment. The mean maximal depth of S-T depression was reduced to 1.7 ± 0.2 mm (p <0.01) and the number of episodes of S-T depression was reduced to 9 ± 2 (p <0.01). The glyceryl trinitrate consumption was reduced significantly (p <0.01), 2.2 ± 0.9 tablets/week during therapy with verapamil.

The systolic time intervals and other indexes of left ventricular function were not altered with verapamil treatment. One patient had pedal edema after 2 weeks on verapamil and after the trial was maintained on verapamil and diuretic drugs without any further deterioration. No conduction defects were noted during this trial. Minor adverse effects included constipation in 6 patients, headache in 2, and giddiness in 1. None were severe enough to warrant withdrawal of treatment.

Nifedipine (Fig. 1 to 3): Of the 28 patients who completed the study, 8 became angina-free on treatment with nifedipine. The exercise time ranged from 3.0 to 12.5 minutes (mean 7.9 ± 0.5). The mean was significantly higher than with placebo (p <0.001) but significantly lower than with verapamil (p <0.01). The resting heart rate was 77 ± 2 beats/min and the maximal heart rate 130 ± 3 beats/min. The heart rate gain was 6.7 beats/min during exercise and the recovery of heart rate in the postexercise period was 46 beats/min. The heart rate at the same exercise time as placebo was 117 ± 3 beats/min. The standing systolic blood pressure at rest was 108 ± 6 mm Hg (p = NS), and the peak systolic blood pressure on exercise was 122 ± 8 mm Hg (p = NS). The peak double product was 159 ± 8 units and the double product at the same exercise time as placebo was reduced to 130 ± 5 units (p <0.01).

The maximal S-T depression in lead CM5 was 2.0 ± 0.2 mm. The 1 and 2 mm times showed an improvement at 5.8 ± 0.4 and 7.5 ± 0.4 minutes, respectively. The S-T depression at the same exercise time as placebo was reduced to 1.0 ± 0.2 mm. The S-T segment recovery was

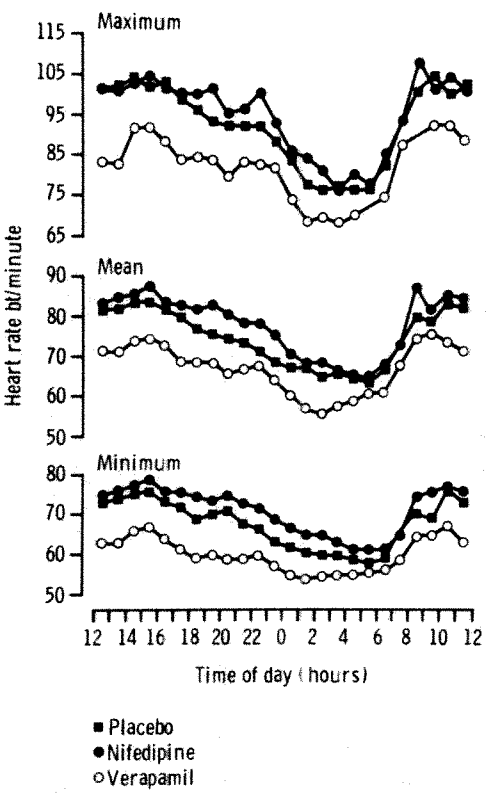

FIGURE 4. Pooled hourly minimal, mean, and maximal heart rates obtained by 24 hour Holter monitoring during placebo, nifedipine, and verapamil therapy. Note the consistent increase in all the heart rate variables on nifedipine therapy and significant bradycardia on verapamil therapy as compared with placebo. bt = beats.

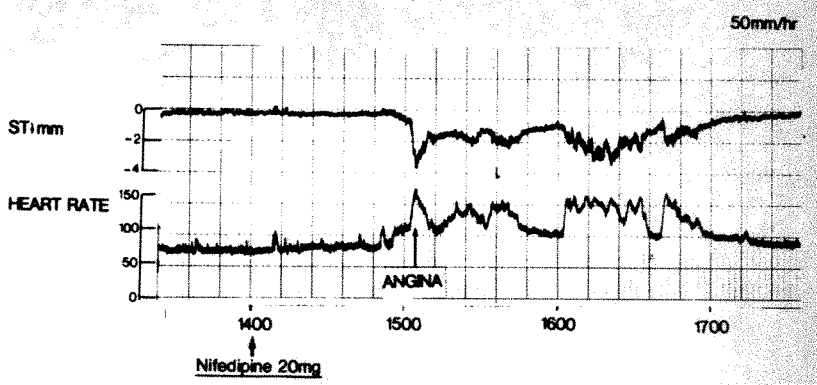

FIGURE 5. An analog trend plot of S-T segment depression associated with marked tachycardia and angina 1 hour after taking 20 mg of nifedipine. The patient was resting during this period. The horizontal axis shows clock time and the vertical axis, calibrated heart rate and S-T depression. The patient took nifedipine at 1400 hours and complained of angina at 1505 hours. Note the increased heart rate and S-T depression lasting almost 2 hours.

1.5 ± 0.2 mm. The S-T segment variables corrected for the increased exercise capacity showed a significant reduction. Lead CC5 showed similar changes.

Twenty-four hour ambulatory monitoring revealed a mild but consistent increase in mean hourly heart rate compared with placebo. The mean number of minutes in which the heart rate exceeded 100 beats/min was 101 ± 10, and this was significantly higher than with both placebo ($p < 0.01$) and verapamil ($p < 0.001$). The mean maximal depth of S-T depression was unaltered at 2.1 ± 0.2 mm, and the number of episodes of S-T depression was 15 ± 2. The glyceryl trinitrate consumption was reduced to 7.2 ± 1.8 tablets/week, but this did not reach statistical significance. The systolic time intervals and other indexes of left ventricular function were not altered with nifedipine therapy.

Three patients had to be withdrawn from the trial during the nifedipine phase without completing 2 weeks of treatment. One patient had accelerated unstable angina that required intraaortic balloon pumping. Another had severe muscular weakness and tremor that disappeared within 24 hours after withdrawal of treatment. The 3rd patient had swelling of the legs, palpitations, and severe headache. Four more patients were withdrawn because of palpitations and angina after taking the drugs, and headache after completing 2 weeks of therapy and all assessments. The ambulatory monitoring of 1 of these patients is shown in Figure 5. There was a rapid increase in heart rate starting about 45 minutes after taking the drug and persisted for about 2 hours. This was accompanied by S-T segment depression and angina. Minor adverse effects not necessitating withdrawal included flushing, tremors, mild pedal edema, and palpitations.

Discussion

Slow calcium channel blocking agents are a heterogeneous group of compounds, with a common action of inhibiting or blocking the slow inward movement of calcium ions across the cell membrane during systole.[18,19] Their site of action is limited to the cell membrane but unlike the beta-adrenoceptor blocking agents, the slow calcium channel blocking drugs vary greatly in chemical structure, pharmacologic action, and pharmacokinetics.[20–22] They have recently been released for general use in the United States, but have been in clinical use in Europe for a long time.[3] Verapamil was one of the first calcium blockers to be used therapeutically, and nifedipine has rapidly gained popularity over the last decade.[23] This study was specifically designed to evaluate objectively the differences in action, efficacy, and safety of these 2 drugs.

Verapamil was first reported by Neumann and Luisada[24] to possess antianginal properties. In their double-blind trial, the drug was administered in a dose of 40 mg 3 times daily and evaluated against placebo in 30 patients with stable angina. Even though a reduction in consumption of nitroglycerin was demonstrated, the study lacked objective end points and therefore no valid conclusions could be drawn. Further studies with objective end points by Sandler et al.,[25] Livesley et al.,[26] and a Danish multicenter group[27] clearly demonstrated that verapamil had an active antianginal action. We performed a single-blind study and double-blind crossover trial of verapamil against placebo in 28 patients, which showed that the drug was more effective than placebo in increasing exercise tolerance and reducing S-T segment changes when used in adequate dosage (360 mg daily).[28,29] We also compared the effects of propranolol with verapamil in a randomized double-blind crossover trial in 22 patients,[30] and investigated the long-term efficacy of verapamil over 1 year,[31] and the potential efficacy and safety of combination with propranolol.[32] Our data, accumulated over 5 years in 100 patients using clearly defined end points, have confirmed that verapamil is a potent and safe antianginal agent.[33–35]

A number of reports have suggested that nifedipine administered orally or sublingually similarly delays the onset of ischemic pain induced by treadmill exercise and minimizes electrocardiographic changes.[36,37] However, in most of these reports,[38,39] the number of patients was small and the control data were inadequate. Ellrodt et al.[3] believed that the data for efficacy of nifedipine in exertional angina were suggestive rather than conclusive. They also commented on the importance of comparing the antianginal efficacy of nifedipine with that of other slow calcium channel inhibitors and with beta-adrenoceptor blocking agents, using adequate numbers of patients and stringently designed protocols with objective end points as test variables. They com-

mented that only data from such comparative studies would permit definition of the role of nifedipine and other slow calcium channel inhibitors in the management of chronic stable angina.

We planned this prospective trial with great care to yield as many objective end points as possible. The trial protocol consisted of a single blind placebo run-in for 2 weeks, after which the patients entered the double-blind randomized crossover phase. Exercise tests, 24 hour ambulatory monitoring, and evaluation of left ventricular function were performed before starting the trial, at the end of the placebo phase, and at the end of each crossover phase. This enabled comparison of the efficacy of each drug with placebo and with each other.

The protocol for exercise testing was carefully designed to minimize subjective bias and observer variation.[40] The entire test was automated, the speed and gradient of the treadmill being controlled by a computer program. Two bipolar electrocardiographic leads were continuously monitored and recorded during and after exercise. The heart rate and S-T segment values were continuously computed and printed out every minute. From these data a number of variables were derived to identify precisely the effects of the drugs on exercise tolerance, onset of S-T segment depression, total S-T segment change, resting, peak and postexercise heart rate, and the double product. Interpatient repeatability of the exercise test was ensured by calibrating the speed and gradient of the treadmill regularly, controlling the laboratory temperature at 24 ± 2°C (mean ± range) and conducting all the tests 90 to 150 minutes after drug administration in the postabsorptive state.

The second leg of the trial was 24 hour monitoring designed to examine the response to uncontrolled environmental influences in these patients. Here again great care was taken to ensure objectivity of results. The tape recorder used was a frequency-modulated machine with an extended low frequency response; we have previously reported our validation of this instrument for S-T data collection.[11] The variables from the tapes were derived by a custom-built computer program. The data included mean, minimal, and maximal hourly heart rates, and S-T segment depression every minute. From the hourly mean heart rates, the number of episodes of S-T depression and the maximal depth of S-T depression could be calculated easily.[41,42]

The effects of both drugs on myocardial contractility were assessed by systolic time intervals, and their effects on the conducting tissue by scanning the ambulatory tapes for prolongation of P-R interval. Neither drug showed any significant change in these variables.

The trial demonstrated a clear difference in the antianginal efficacy of the 2 calcium antagonists in the doses used. Verapamil was more effective in increasing exercise tolerance, decreasing the S-T segment changes and increasing the time required for onset of S-T depression. It produced mild resting bradycardia and a marked reduction in exercise-induced tachycardia. This action on the heart rate was confirmed by the ambulatory heart rates, which showed that during verapamil therapy the mean heart rate exceeded 100 beats/min in only 4 ± 0.2 minutes in 24 hours, as compared with 45 ± 1.2 min/24 hours while on placebo. This effect on the exercise heart rate combined with the slow channel blocking activity appears to be the main basis for the antianginal activity of the drug.

By contrast, the effects of nifedipine varied. The drug produced mild tachycardia and only a moderate improvement in exercise tolerance and S-T segment variables. Adverse effects were frequent, even with the dose of 20 mg 3 times daily used in this trial; the most interesting adverse effect was the development of symptomatic angina with tachycardia appearing within 60 to 90 minutes of taking a 20 mg dose. This occurred in 7 patients, and we objectively demonstrated tachycardia associated with marked S-T depression by ambulatory monitoring in all of them. Similar findings have been reported by other investigators.[43–46] The relatively poor results with nifedipine in comparison with verapamil may be due to this increase in heart rate, which might be controlled by adding a beta-adrenoceptor blocking drug.

The design of this study included fixed doses as an essential feature, and it could be that different results would be obtained with larger doses. However, the doses chosen were based on experience of other extensive trials which suggested that these would be the most effective dosages with minimal adverse effects.

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Hemodynamic and Electrophysiologic Effects of Verapamil And Nifedipine in Patients on Propranolol

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Because the combined use of a beta-adrenergic blocking agent and a calcium antagonist may be beneficial in patients with severe angina, we assessed the hemodynamic and electrophysiologic effects of verapamil or nifedipine in patients receiving oral propranolol. In 26 patients with stable angina receiving oral propranolol (234 ± 230 mg/day, mean ± standard deviation), cardiac catheterization was performed, and variables were measured at baseline and 5 to 10 minutes after (1) intravenous saline solution, 10 ml (n = 6); (2) intravenous verapamil, 0.15 mg/kg body weight to a maximal dose of 10 mg (n = 10); and (3) sublingual nifedipine, 10 mg (n = 10). Cardiac output (by thermodilution) was unchanged after saline solution and verapamil but increased with nifedipine (4.3 ± 1.1 to 5.0 ± 1.4 liters/min, p <0.05). Mean arterial pressure did not change with saline solution or nifedipine but decreased with verapamil. Peak-positive dP/dt was reduced only by verapamil (from 1,086 ± 175 to 926 ± 167 mm Hg/s, p <0.05). Coronary sinus blood flow (by thermodilution) was not altered by saline solution, nifedipine, or verapamil. Verapamil reduced the heart rate (from 63 ± 8 to 60 ± 9 beats/min, p <0.05) and increased the A-H interval (from 108 ± 14 to 129 ± 23 ms, p <0.05). In contrast, nifedipine increased the heart rate (from 65 ± 8 to 71 ± 8 beats/min, p <0.05) but did not change the A-H interval. Left ventricular ejection fraction (by radionuclide ventriculography) was unaltered by saline solution or verapamil but increased with nifedipine (from 0.52 ± 0.13 to 0.57 ± 0.13, p <0.05). In summary, when administered to patients with normal or only mildly depressed left ventricular function who are receiving oral propranolol, nifedipine improves cardiac output and left ventricular ejection fraction without affecting intracardiac filling pressure or atrioventricular conduction. In contrast, verapamil diminishes left ventricular contractility and slows atrioventricular conduction. Thus, the combination of verapamil and propranolol must be used with caution in patients with underlying left ventricular dysfunction or conduction system disease.

The beta-adrenergic blocking agents are efficacious in the treatment of most patients with stable angina pectoris.[1–3] By reducing the heart rate, systolic arterial pressure, and left ventricular contractility, these agents diminish myocardial oxygen demands. More recently, the calcium antagonists, including verapamil and nifedipine, have been shown to exert a potent antianginal effect.[4–8] Like the beta-adrenergic blocking drugs, these agents reduce myocardial oxygen requirements[8–12]; in addition, they may diminish coronary vascular resistance and augment coronary blood flow.[8,12–15] For the patient whose angina is not controlled by beta blockade or calcium blockade alone, a combination of these agents may be particularly effective because their mechanisms of action are, in some ways, complementary. In fact, initial clinical studies have shown that nifedipine and propranolol[16,17] as well as verapamil and propranolol[18] are beneficial in patients with severe angina.

Although combined beta-adrenergic and calcium blockade is potentially beneficial to the patient with severe angina, only a few studies have attempted to define the hemodynamic and electrophysiologic consequences of such combination therapy.[19–22] These

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TABLE I Hemodynamic Variables Before and After Drug Administration

Variable	Saline Solution		Verapamil		Nifedipine	
	Before	After	Before	After	Before	After
Cardiac output (liters/min)	4.2 ± 1.2	4.2 ± 1.2 a	4.5 ± 0.7	4.4 ± 1.0 a	4.3 ± 1.1	5.0 ± 1.4* b
Coronary sinus blood flow (ml/min)	104 ± 65	108 ± 64 a	123 ± 30	131 ± 61 a	127 ± 71	146 ± 95 a
Pressures (mm Hg)						
Femoral arterial mean	95 ± 13	98 ± 14 a	98 ± 7	87 ± 10 b	100 ± 17	94 ± 12 ab
Right atrial mean	6 ± 2	5 ± 2 ab	5 ± 2	7 ± 2* b	6 ± 2	6 ± 2 a
Pulmonary capillary wedge mean	10 ± 4	11 ± 4 a	10 ± 2	13 ± 3* a	11 ± 2	11 ± 3 a
Resistances (dynes s cm^{-5})						
Systemic vascular	1,788 ± 494	1,869 ± 510 a	1,667 ± 296	1,513 ± 251* ab	1,881 ± 704	1,505 ± 474* b
Pulmonary arteriolar	129 ± 52	137 ± 58 a	145 ± 60	157 ± 69 a	148 ± 61	157 ± 42 a
LV + dP/dt (mm Hg/s)	1,091 ± 210	1,081 ± 215 a	1,086 ± 175	926 ± 167* b	1,092 ± 190	1,109 ± 185 a

* $p < 0.05$ in comparison with the same pharmacologic agent in the baseline state.
By analysis of variance, those figures marked with the same letter (a or b) are statistically indistinguishable at $p = 0.05$; those marked with different letters are statistically distinguishable at $p < 0.05$.

TABLE II Electrophysiologic and Scintigraphic Variables Before and After Drug Administration

Variable	Saline Solution		Verapamil		Nifedipine	
	Before	After	Before	After	Before	After
Heart rate (beats/min)	60 ± 8	60 ± 9 a	63 ± 8	60 ± 9* a	65 ± 8	71 ± 8* b
A-H interval (ms)	90 ± 27	89 ± 22 a	108 ± 14	129 ± 23* b	113 ± 24	115 ± 23 a
H-V interval (ms)	59 ± 9	57 ± 8 a	51 ± 15	50 ± 12 a	49 ± 11	49 ± 11 a
LVEDVI (ml/m^2)	106 ± 45	106 ± 38 a	102 ± 29	105 ± 32 a	85 ± 21	87 ± 22 a
LVESVI (ml/m^2)	55 ± 25	58 ± 26 a	55 ± 19	54 ± 20 a	45 ± 19	42 ± 20* a
LVEF	0.51 ± 0.06	0.49 ± 0.09 a	0.49 ± 0.10	0.50 ± 0.09 ab	0.52 ± 0.13	0.57 ± 0.13* b

See Table I for an explanation of statistical indicators.
LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index.

preliminary investigations have suggested that verapamil and nifedipine can be administered safely to the patient already receiving propranolol, but the effects of a verapamil-propranolol combination may differ substantially from those of combined nifedipine and propranolol. The present study was performed to compare the acute hemodynamic and electrophysiologic effects of intravenous verapamil with those of sublingual nifedipine in patients receiving oral propranolol.

Methods

Study patients: The study was performed in 26 consecutive persons (18 men and 8 women, mean age 54 years) referred for cardiac catheterization for the evaluation of chest pain, all of whom were receiving oral propranolol (mean dose 234 mg/day; range 40 to 1,280). In each patient data acquisition was performed 2 to 3 hours after a regularly scheduled dose of oral propranolol. Informed consent was obtained from all patients. Patients with valvular or congenital heart disease, left bundle branch block, or previous coronary arterial bypass surgery were excluded.

Protocol: In each patient, hemodynamic, electrophysiologic, and (in 15 patients) radionuclide ventriculographic measurements were made (1) in the baseline state (that is, on propranolol alone), and (2) after random administration of 1 of 3 pharmacologic agents. All data acquisition was performed before angiography.

Control group ($n = 6$): In these subjects, baseline measurements were accomplished, after which 10 ml of normal saline solution was administered intravenously. Subsequently, all measurements were repeated 5 to 10 minutes later. This group comprised 4 men and 2 women with an average age of 51 years. Their daily propranolol dosage was 177 ± 92 mg (mean ± standard deviation) (range 60 to 320). Coronary arteriography revealed single vessel coronary arterial disease (defined as 70% or greater luminal diameter narrowing) in 3 and triple vessel disease in 3.

Verapamil group ($n = 10$): In these patients, baseline measurements were made, then verapamil (Knoll Pharmaceutical, Whippany, New Jersey), 0.15 mg/kg to a maximal dose of 10 mg, was administered intravenously. All measurements were repeated 5 minutes after administration of verapamil. These 10 patients included 8 men and 2 women with a mean age of 54 years. Their daily propranolol dose was 298 ± 352 mg (range 80 to 1,280). At coronary arteriography 3 had single vessel coronary arterial disease, 3 had double vessel disease, and 4 had triple vessel disease.

Nifedipine group ($n = 10$): After baseline measurements were performed, nifedipine (Bayer Pharmaceutical, Munich, Germany) (10 mg) was administered sublingually, and all measurements were repeated 10 minutes later. Of these 10 patients, 6 were men and 4 were women, with an average age of 54 years. Their daily propranolol dose was 204 ± 104 mg (range 40 to 360). Three had single vessel coronary artery disease, 1 had double vessel disease, and 6 had triple vessel disease.

Variables assessed: *Hemodynamic measurements:* Systemic arterial pressure was recorded through a percutaneous femoral arterial cannula. Left ventricular pressure was recorded with a high fidelity micromanometer-tipped pigtail catheter (Millar Instruments, Houston) advanced to the left ventricle from the femoral artery, and the maximal first derivative of left ventricular pressure (dP/dt) was electronically derived from this pressure trace. Right atrial, pulmonary ar-

terial, and pulmonary capillary wedge pressure as well as forward cardiac output were measured with a flow-directed, balloon-tipped thermodilution catheter (Electronics for Medicine, model 62 00 37) advanced from the femoral vein. An average of 3 to 4 thermodilution measurements of cardiac output was used for the final computations. The variability of thermodilution measurements in our laboratory is ±4%. From these data, systemic and pulmonary arteriolar resistance was calculated.

Coronary blood flow measurements: In each patient, a thermodilution catheter (model CCS-7U-90B, Wilton Webster Laboratories, Altadena, California) was advanced to the coronary sinus from the right basilic vein, and its position was confirmed oximetrically and by the injection of 3 to 5 ml of contrast material. Coronary sinus blood flow was measured with the continuous thermodilution technique.[23]

Electrophysiologic measurements: A tripolar pacing catheter was advanced from the femoral vein and positioned across the tricuspid valve, and atrio-His bundle (A-H) and His bundle-ventricular (H-V) conduction times were measured.[24]

Radionuclide ventriculography: In 15 of the 26 patients, red blood cells were labeled with 30 mCi of technetium-99m sodium pertechnetate using a technique combining features of both in vitro and in vivo labeling.[25] In the remaining 11 patients, radionuclide ventriculography was not performed because the necessary imaging equipment was not available. Scintigraphic data collection was performed with a portable gamma scintillation camera (Series Sigma 420, Ohio Nuclear, Solon, Ohio), as previously described.[26–30] Left ventricular volume and ejection fraction were estimated by a totally nongeometric technique developed and validated in our laboratory.[28–30] All volumes were normalized for body surface area. The inter- and intraobserver variability of these volume measurements in our laboratory is 7.5 and 6%, respectively, and the reproducibility of these measurements over time has been substantiated.[27]

Statistical analysis: All data are reported as mean ± 1 standard deviation. For each variable in the baseline state, the 3 groups were compared with an analysis of variance. For each group (control, verapamil, and nifedipine), each variable at baseline and after drug administration was evaluated with a paired *t* test.[31] This analysis of paired data was performed (1) for the complete groups (6 control subjects, 10 taking verapamil and 10 taking nifedipine) and (2) after excluding the 4 patients who were receiving either a small (less than 100 mg/day) or large (more than 500 mg/day) dose of propranolol (5 control subjects, 8 taking verapamil, and 9 taking nifedipine). In addition, for each variable in each patient, the difference between the value of baseline and after drug administration was determined, and these differences were compared among the 3 groups by analysis of variance. For all analyses, a p value less than 0.05 was considered significant.

Results

In the baseline state, the 3 groups were similar with regard to age, severity of coronary artery disease, propranolol dosage, and all hemodynamic, electrophysiologic, and scintigraphic variables (Tables I and II). Three patients (1 from each group) were receiving less than 100 mg/day of propranolol, and 1 patient in the verapamil group was receiving an unusually large dose of propranolol (1,280 mg/day). With the exclusion of these 4 patients, the control group (n = 5) received a

TABLE III Hemodynamic Variables Before and After Drug Administration in the 22 Patients Receiving 100 to 360 mg/Day of Propranolol

Variable	Saline		Verapamil		Nifedipine	
	Before	After	Before	After	Before	After
Cardiac output (liters/min)	4.4 ± 1.3	4.4 ± 1.2	4.7 ± 0.5	4.7 ± 0.8	4.2 ± 1.0	4.8 ± 1.2*
Coronary sinus blood flow (ml/min)	115 ± 66	118 ± 66	121 ± 32	136 ± 64	121 ± 73	143 ± 100
Pressures (mm Hg)						
Femoral arterial mean	98 ± 11	102 ± 11	99 ± 7	90 ± 7*	102 ± 17	95 ± 12
Right atrial mean	6 ± 2	6 ± 2	5 ± 2	7 ± 2*	6 ± 3	6 ± 2
Pulmonary capillary wedge mean	10 ± 4	12 ± 4	10 ± 2	13 ± 3*	11 ± 3	10 ± 3
Resistances (dynes s cm^{-5})						
Systemic vascular	1,796 ± 552	1,873 ± 570	1,608 ± 257	1,455 ± 236*	1,966 ± 690	1,577 ± 441*
Pulmonary arteriolar	136 ± 55	140 ± 64	136 ± 49	133 ± 37	154 ± 63	165 ± 33
LV dP/dt (mm Hg/s)	1,092 ± 243	1,081 ± 248	1,132 ± 163	980 ± 129*	1,104 ± 198	1,123 ± 191

* $p < 0.05$ in comparison with the same pharmacologic agent in the baseline state.

TABLE IV Electrophysiologic and Scintigraphic Variables Before and After Drug Administration in the 22 Patients Receiving 100 to 360 mg/Day of Propranolol

Variable	Saline Solution		Verapamil		Nifedipine	
	Before	After	Before	After	Before	After
Heart rate (beats/min)	60 ± 9	61 ± 9	65 ± 6	62 ± 7	66 ± 9	71 ± 9*
A-H Interval (ms)	80 ± 17	81 ± 15	107 ± 13	131 ± 24*	117 ± 23	118 ± 23
H-V Interval (ms)	57 ± 9	55 ± 9	53 ± 17	53 ± 16	50 ± 11	50 ± 11
LVEDVI (ml/m^2)	106 ± 45	106 ± 38	98 ± 32	106 ± 35*	85 ± 21	87 ± 22
LVESVI (ml/m^2)	55 ± 25	58 ± 26	52 ± 23	56 ± 23	45 ± 19	42 ± 20*
LVEF	0.51 ± 0.06	0.49 ± 0.09	0.50 ± 0.11	0.50 ± 0.10	0.52 ± 0.13	0.57 ± 0.13*

* $p < 0.05$ in comparison with the same pharmacologic agent in the baseline state.
Abbreviations as in Table II.

daily propranolol dose of 200 ± 80 mg (range 120 to 320); the verapamil group (n = 8) received 203 ± 66 mg (range 100 to 320); and the nifedipine group (n = 9) received 222 ± 92 mg (range 120 to 360). For these 22 patients, the baseline characteristics of the 3 patient groups were similar (Tables III and IV).

Hemodynamic alterations: The hemodynamic alterations induced by saline solution, verapamil, and nifedipine for all 26 patients are shown in Table I. Cardiac output did not change with the administration of saline solution or verapamil. In contrast, nifedipine caused a significant increase in cardiac output (Fig. 1). Systemic arterial pressure was not altered by saline solution or nifedipine but was reduced by verapamil; however, the reduction in arterial pressure produced by verapamil did not differ statistically from that produced by nifedipine (Table I). Systemic vascular resistance did not change with saline solution but decreased with both calcium antagonists (Fig. 1).

Mean right atrial pressure was unchanged with saline solution and nifedipine but increased slightly with verapamil, and pulmonary capillary wedge pressure behaved similarly. These changes in right atrial and pulmonary capillary wedge pressure induced by verapamil were not significantly different from those produced by saline solution (Table I). Peak positive left ventricular dP/dt was not altered by saline solution or nifedipine but was reduced by verapamil (Fig. 2).

The results for the 22 patients receiving 100 to 360 mg/day of propranolol are shown in Table III. The hemodynamic changes induced by each of the 3 pharmacologic agents are similar to those described for the entire group.

Effects on coronary sinus blood flow: Coronary sinus blood flow was not altered by any pharmacologic agent (Tables I and III).

Electrophysiologic alterations: For the entire group of 26 patients, verapamil and nifedipine produced opposite effects on the heart rate: it decreased with verapamil and increased with nifedipine (Table II, Fig. 3). However, the reduction in heart rate produced by verapamil was not statistically different from that produced by saline solution. For the smaller group of 22 patients, the reduction in heart rate induced by verapamil did not achieve statistical significance (Table IV). The A-H interval was not altered by saline solution or nifedipine but was prolonged by verapamil (Tables II and IV, Fig. 3). None of the 3 agents altered the H-V interval.

Scintigraphic alterations: Left ventricular end-diastolic volume index was unchanged by the 3 agents (Tables II and IV). End-systolic volume index decreased

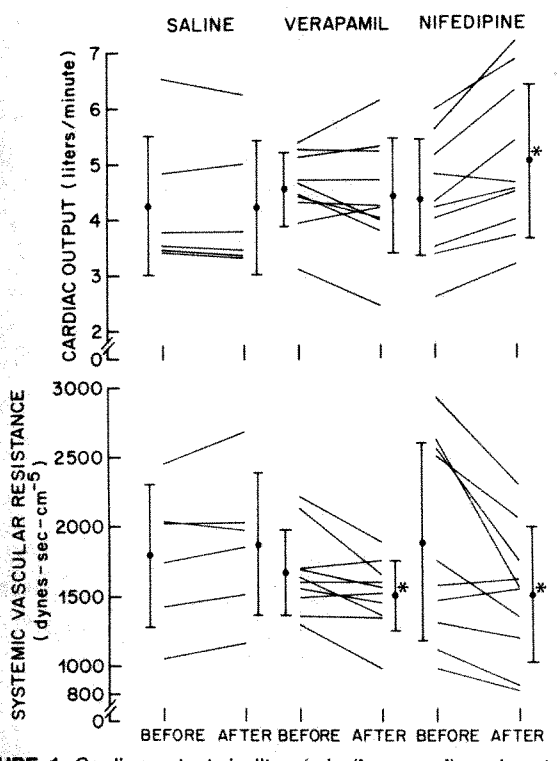

FIGURE 1. Cardiac output, in liters/min (**top panel**), and systemic vascular resistance, in dynes-sec-cm^{-5} (**bottom panel**), before and after the administration of saline solution (**left**), verapamil (**middle**), or nifedipine (**right**). Each **line** represents the data from 1 patient, and the means ± 1 standard deviation are shown on either side of each set of lines. Cardiac output was unchanged by saline solution or verapamil but increased significantly with administration of nifedipine. Systemic vascular resistance was reduced by verapamil and nifedipine. **Asterisks** indicate $p < 0.05$ in comparison with the values before drug administration.

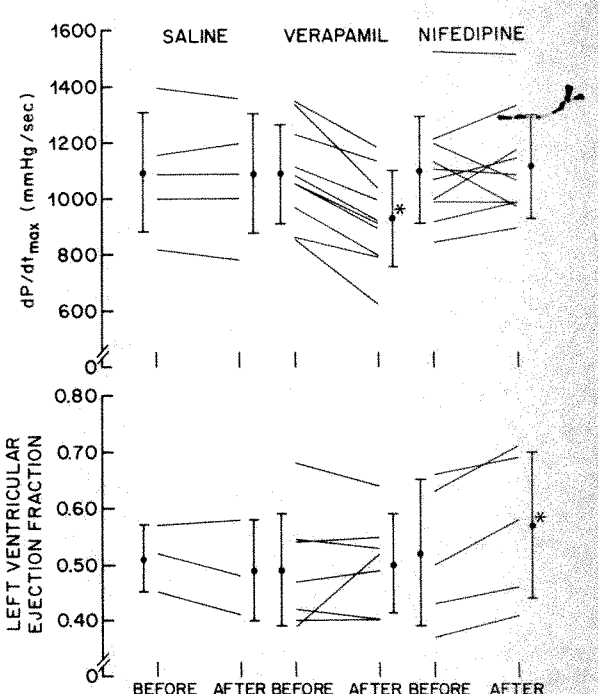

FIGURE 2. Left ventricular peak positive dP/dt, in mm Hg/s (**top panel**), and left ventricular ejection fraction (**bottom panel**), before and after the administration of saline solution (**left**), verapamil (**middle**), or nifedipine (**right**). Each **line** represents the data from 1 patient, and the means ± 1 standard deviation are shown on either side of each set of lines. Left ventricular dP/dt was reduced by verapamil; ejection fraction increased after administration of nifedipine. **Asterisks** indicate $p < 0.05$ in comparison with the same pharmacologic agent before drug administration.

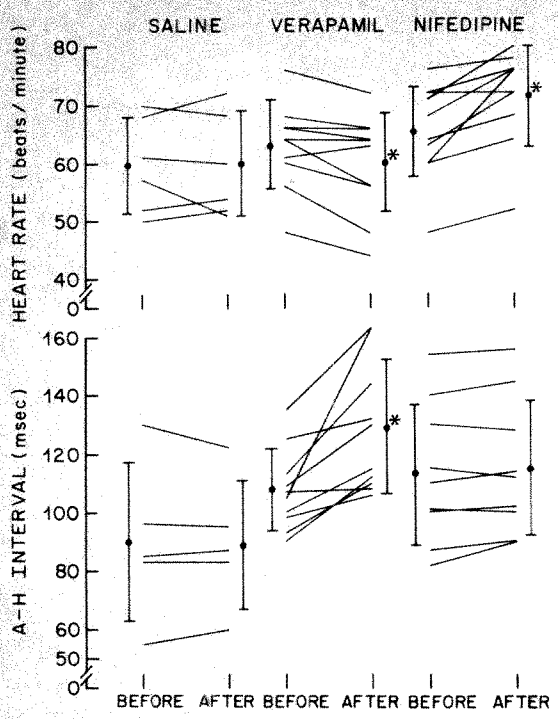

FIGURE 3. Heart rate, in beats/min (**top panel**), and A-H interval, in milliseconds (ms) (**bottom panel**), before and after the administration of saline solution (**left**), verapamil (**middle**), or nifedipine (**right**). Each **line** represents the data from 1 patient, and the means ± 1 standard deviation are shown on either side of each set of lines. The heart rate was reduced by verapamil and increased by nifedipine. The A-H interval was lengthened only by verapamil. **Asterisks** indicate $p < 0.05$ in comparison with the same pharmacologic agent before drug administration.

with nifedipine. Left ventricular ejection fraction was not affected significantly by saline solution or verapamil but increased with nifedipine (Tables II and IV, Fig. 2).

Adverse effects: In one patient who received verapamil, mean systemic arterial pressure decreased from 93 to 68 mm Hg. The heart rate failed to increase, and cardiac output decreased from 3.1 liters/min to 2.4 liters/min. All values returned to baseline within 15 to 20 minutes. This patient was receiving a large daily dose of propranolol (1,280 mg). With this exception, all patients tolerated saline solution, verapamil, and nifedipine without difficulty.

Discussion

Preliminary clinical trials have suggested that the combination of a beta-adrenergic blocking agent and a calcium antagonist may be more effective than either agent alone in the treatment of patients with severe angina.[16–18] The beta-adrenergic blocking agents such as propranolol diminish myocardial oxygen demands by reducing the heart rate, systemic arterial pressure, and left ventricular contractility, but they do not increase the myocardial oxygen supply.[32,33] The calcium antagonists such as verapamil and nifedipine also reduce myocardial oxygen demands (primarily by diminishing afterload); in addition, they augment coronary blood flow by reducing coronary vascular resistance.[8,12,13] Because these agents exert their beneficial effects by different mechanisms, their combination may produce an especially salutary influence on the balance between myocardial oxygen supply and demand.

However, at the same time, combination beta-blocking calcium antagonist therapy could theoretically produce adverse effects. For example, in the patient not receiving a beta-blocking agent, verapamil's negative inotropic and chronotropic influence is counteracted, at least in part, by a reflex increase in sympathetic tone.[34] In the presence of beta blockade this reflex response may be blunted, leading to a reduction in left ventricular performance and cardiac output. Alternatively, in the absence of a beta-blocking drug, nifedipine's powerful effects as a peripheral arterial dilator are partially offset by a compensatory increase in heart rate. In the presence of a beta-blocking agent this reflex tachycardia could be prevented, leading to profound hypotension.[35] Because it is unclear whether the potential beneficial effects of combined beta-blocking calcium antagonist therapy outweigh its potential adverse effects, the present study was performed to explore the hemodynamic and electrophysiologic effects of verapamil and nifedipine in patients already receiving propranolol.

Hemodynamic alterations: In the absence of beta-adrenergic blockade, both verapamil and nifedipine reduce systemic arterial pressure and resistance.[9,10,19,22,34] Because nifedipine is an especially potent vasodilator, it elicits a strong reflex sympathetic response, which offsets its intrinsic negative inotropic effects, so that left ventricular dP/dt may even increase.[36] As a result, nifedipine alone augments cardiac output and left ventricular ejection fraction, even in patients with underlying left ventricular dysfunction.[10,37] In contrast, verapamil causes a decrease in left ventricular dP/dt[38] and a modest increase[34] or no change[22,38] in cardiac output. Its effect on left ventricular ejection fraction is not clear: some studies have demonstrated a decrease,[18] others have shown no change,[37,39] and yet others have shown an increase in this variable.[34]

Although previous studies have attempted to assess the hemodynamic effects of verapamil or nifedipine in patients already receiving beta-adrenergic blocking agents, they have produced conflicting results. Packer et al.[22] administered oral verapamil (120 mg) to patients receiving long-term propranolol therapy and noted a decrease in cardiac index and mean arterial pressure as well as an increase in pulmonary capillary wedge pressure. When this same dose of verapamil was readministered after withdrawal of propranolol, the cardiac index and wedge pressure did not change. Leon et al.[21] noted that a verapamil-propranolol combination produced a reduction in both left ventricular ejection fraction and ejection rate at rest, although verapamil alone produced a similar diminution in ejection fraction. In contrast, Kieval et al.[20] showed that a verapamil-propranolol combination caused no change in cardiac index, left ventricular end-diastolic pressure, left ven-

tricular ejection fraction or maximal dP/dt. Finally, in 12 patients receiving atenolol, Joshi et al.[19] observed no increase in left ventricular ejection fraction and a decrease in dP/dt after administration of nifedipine.

In our study, verapamil or nifedipine was administered on a short-term basis to patients already receiving long-term oral propranolol. Although we made no attempt to ensure full beta-adrenergic blockade in these patients, their dosages of propranolol were those commonly used for the treatment of angina pectoris. Even in the presence of propranolol, nifedipine caused an increase in cardiac output and left ventricular ejection fraction as well as no change in left ventricular dP/dt or intracardiac filling pressure (Tables I and III, Fig. 1 and 2). In contrast, verapamil caused no change in cardiac output or ejection fraction and a decrease in left ventricular dP/dt. In 1 patient (who was taking 1,280 mg/day of propranolol), verapamil induced a sizeable decrease in cardiac output and systemic arterial pressure. Thus, the combination of verapamil and propranolol must be used cautiously, especially in persons who are taking particularly large doses of the latter agent.

Changes in coronary blood flow: The effect of verapamil or nifedipine on coronary blood flow represents a balance between direct coronary vasodilation and reflex vasoconstriction caused by a decrease in myocardial oxygen demands. In most studies verapamil or nifedipine administered alone has caused an increase in coronary blood flow, although Ferlinz et al.[9] demonstrated a slight decrease in coronary blood flow with verapamil. In the present study neither verapamil nor nifedipine caused a significant change in coronary sinus blood flow (Tables I and III).

Electrophysiologic changes: The negative chronotropic effect of nifedipine, like its negative inotropic effect, is offset in vivo by reflex mechanisms, so that nifedipine alone increases heart rate. Atrioventricular conduction is unaltered.[40] In contradistinction, verapamil exerts a powerful negative chronotropic effect, so that there is no reflex increase in heart rate despite a reduction in peripheral vascular resistance.[22,34,38] In addition, atrioventricular conduction is impaired.[40] In the present study, the heart rate increased with nifedipine and decreased slightly with verapamil (Tables II and IV, Fig. 3). In addition, verapamil prolonged the A-H interval in all patients, whereas nifedipine exerted no effect on this variable. Thus, the combination of verapamil and propranolol must be used cautiously in patients with underlying conduction system disease.

In short, the hemodynamic and electrophysiologic alterations induced by verapamil and nifedipine in patients already receiving propranolol are similar to those induced by these agents in the absence of propranolol. Specifically, the alterations produced by verapamil in this study do not differ from those described by Singh and Roche[38] in patients not receiving a beta-adrenergic blocking agent; similarly, the combination of nifedipine and propranolol caused hemodynamic and electrophysiologic changes resembling those induced by nifedipine alone.

Limitations of the present study: This study is limited in several ways. First, it examines the hemodynamic and electrophysiologic effects of a single dose of intravenous verapamil or sublingual nifedipine in patients already receiving long-term oral propranolol. It makes no attempt to assess these effects during the long-term administration of both a calcium antagonist and a beta-adrenergic blocking agent. It is conceivable that the long-term administration of both agents may induce hemodynamic and electrophysiologic effects different from those described in our study. Second, both verapamil and nifedipine were administered in a standardized dose. Although the dosages of each were similar to those used in previous studies,[4,13,15,38,41] it is possible that different effects may be produced by different amounts of each agent. For example, it is possible that a larger dose of nifedipine (that is, 20 mg) could produce adverse effects not observed after 10 mg. Similarly, a smaller dose of verapamil (that is, 0.025 to 0.10 mg/kg) would be expected to exert a lesser effect on contractility and cardiac conduction. Third, most of the patients in the present study had normal or only slightly impaired left ventricular function at rest (Tables I to IV, Fig. 2); it is certainly possible that those with more severe left ventricular dysfunction may respond differently to the combination of propranolol and a calcium antagonist, either verapamil or nifedipine. Lastly, all variables were measured only in the resting state, and no attempt was made to assess the effects of combination therapy on hemodynamic or electrophysiologic variables during exercise.

Clinical implications: The combined use of a beta-adrenergic blocking agent and a calcium antagonist may be beneficial in patients with stable angina who continue to be symptomatic despite therapy with either agent alone. When administered to patients already receiving propranolol, verapamil and nifedipine produce hemodynamic and electrophysiologic changes similar to those produced in the absence of propranolol. Nifedipine improves left ventricular performance without affecting cardiac conduction. In contrast, verapamil diminishes left ventricular contractility and slows atrioventricular conduction. Therefore, the combination of verapamil and propranolol must be used with great caution in patients with underlying left ventricular dysfunction or conduction system disease. Although administration of a nifedipine-propranolol combination is probably preferable in these patients, further studies are needed to establish the safety of this combination in patients with severe left ventricular dysfunction.

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Long-Term Follow-Up of Verapamil and Nitrate Treatment for Coronary Artery Spasm

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Thirty-seven patients with coronary artery spasm and minor coronary atherosclerosis (34) or normal coronary arteries (3) were followed up long-term. All had angina at rest, 32 had nocturnal angina, and 13 had a positive exercise test with S-T elevation. Three had a previous subendocardial infarction; 10 had had serious arrhythmias, which caused syncope in 7. At last review, 21 months (range 1 to 61) after starting therapy, 27 patients continued on verapamil, 314 (120 to 600) mg/day; 4 who did not respond to verapamil were taking nifedipine, 58 (30 to 80) mg/day; and 16 were also taking isosorbide dinitrate, 41 (20 to 80) mg/day. Of the 31 patients on therapy, 21 were asymptomatic, 9 were improved (1 to 4 attacks/month), and 1 had an average of 8 anginal attacks/month; the remaining 6 had stopped therapy and 5 were asymptomatic a mean of 10 (3 to 18) months after stopping. The exercise test became negative in all 12 patients tested on therapy, although 3 required nitrates in addition to verapamil or nifedipine.

In 26 supervised treatment withdrawals in the hospital, a mean of 15 (1 to 55) months on therapy, 10 developed angina in less than 48 hours. Angina recurred in all 6 unsupervised, patient-initiated withdrawals. Failure to stop smoking was positively associated with recurrence of angina on treatment withdrawal ($p < 0.02$).

Long-term treatment of coronary artery spasm with verapamil or nifedipine together with isosorbide dinitrate was well tolerated and effectively relieved angina. No documented serious arrhythmias, syncopal episodes, myocardial infarction, or death occurred during follow-up.

Coronary artery spasm may cause spontaneous angina in patients with normal coronary arteries or with insignificant atherosclerotic disease.[1,2] Therapy with beta-adrenergic receptor blocking drugs is ineffective or may aggravate angina.[3,4] Nitrates relieve acute attacks[1,2] but are less effective for chronic therapy. Both uncontrolled and controlled clinical trials have demonstrated that the calcium-antagonist drugs nifedipine,[4,5] diltiazem,[3,6] perhexiline,[7-9] and verapamil[10-14] effectively prevent angina due to coronary spasm, but the long-term results of medical treatment are not known. Because the symptoms of these patients are known to vary cyclically over long periods it is uncertain whether therapy is required indefinitely. This study reports the outcome of treatment in 37 patients with coronary artery spasm followed up for up to 5 years, and the results of treatment withdrawal in 27 of them.

Methods

Patient population: Thirty-seven patients, 28 men and 9 women (mean age 52 ± 7 years) with coronary artery spasm, were included in the study. All patients fulfilled the following diagnostic criteria: (1) a history of recurrent angina at rest; (2) evidence of transient myocardial ischemia (1 mm or greater S-T elevation or depression on the electrocardiogram or reversible defects on thallium perfusion imaging) or angiographically observed coronary spasm during either spontaneous or ergonovine-provoked angina;[15] and (3) less than 70% luminal diameter narrowing in any coronary artery.

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Medical therapy: After diagnosis verapamil therapy was commenced in all patients and the dose was altered according to the symptomatic response. Additional isosorbide dinitrate was given routinely to most patients, and beta receptor blockers were discontinued. Five of the patients who did not respond satisfactorily to verapamil were changed to nifedipine. The patients were followed up for a mean duration of 21 (range 1 to 61) months after starting therapy, 6 for less than 12 months, 18 for 1 to 2 years, and 13 for greater than 2 years. The symptomatic response to treatment was assessed as: (a) good (asymptomatic), (b) satisfactory (1 to 4 attacks of angina per month), or (c) unsatisfactory (more than 4 attacks of angina per month). Seven of the paients with major arrhythmias underwent Holter electrocardiographic monitoring on therapy. Patients with exercise-induced coronary spasm were exercised while on therapy.

Withdrawal from therapy: Twenty-four patients who had responded to therapy for a mean period of 15 (range 1 to 55) months were admitted to the hospital. All therapy, including nitrates, was withdrawn under supervision and S-T segments were monitored for 48 hours. Five other asymptomatic patients discontinued therapy themselves after a mean of 7 (range 2 to 12) months on treatment.

Statistical analysis: Student's t test was used to test for differences in the starting dose of verapamil in those who did and did not require an increase in dose.[16] The exact test of Fisher, Irwin, and Yates[17] was used to determine the significance of differences in proportions of patients with and without recurrent angina on withdrawal of therapy.

Results

Clinical findings (Table I): All 37 patients had had angina at rest for a median period of 5 months (range 1 to 120) before diagnosis. Patients were often incapacitated by angina, and 10 had 10 to 30 episodes weekly. Nocturnal episodes occurred in 32 patients (86%), and 17 (46%) also complained of effort-related angina. Thirty-two patients (86%) were smokers, and 27 of these smoked 20 to 80 cigarettes daily. Hypertension had been treated in 43% with satisfactory control in all. Raynaud's phenomenon and migraine were experienced by approximately one fourth of the patients, and in 4 the 2 conditions coexisted. Anterior subendocardial infarction had occurred in 3. Beta receptor blocking agents had been used before entry to the study in 25 (68%) without improving symptoms, and 16 (43%) were taking nitrates.

Electrocardiographic and angiographic findings (Table II): The resting electrocardiogram was normal in 15 of the 37 patients, while the remainder showed S-T and T wave changes. Twelve lead electrocardiograms recorded during spontaneous angina in 27 showed greater than 1 mm S-T segment elevation in 22 (59%), S-T depression in 4 (11%), and no change in 1. Anterior ischemia predominated. Serious arrhythmias were documented during angina in 10 patients (27%) and caused syncope in 7. Coronary angiography was normal in only 3 patients. In the majority mild coronary atherosclerosis (less than 50% luminal diameter reduction) was present, while 2 patients had stenotic lesions in the range of 50 to 70%.

TABLE I Clinical Features

	Patients	
	n	%
Total	37	...
Men	28	76
Women	9	24
Angina		
At rest	37	100
Nocturnal	32	86
On exertion	17	46
Smokers	32	86
Raynaud's phenomenon	8	22
Migraine	10	27
Hypertension	16	43
Thyrotoxicosis	1	3
Previous myocardial infarction	3	8

Ergonovine testing: Twenty-five ergonovine tests were performed in 21 patients and all were positive (Table III). The mean dose of ergonovine was 0.38 mg (range 0.1 to 0.7). S-T elevation occurred in 17 patients and S-T depression in 2. In 12 of 13 patients with a positive ergonovine test and an electrocardiogram recorded during spontaneous angina, the site of ischemia was the same. The remaining patient showed inferior ischemia after ergonovine but anterior and inferior ischemia spontaneously.

Coronary artery involved by spasm: From the occurrence of spasm at angiography and the localization of ischemia during spontaneous and ergonovine-induced angina, the arteries involved by spasm were as follows: the right coronary artery in 12 patients, the left anterior descending in 19, intermediate in 2, the left circumflex in 1, and both the left anterior descending and right coronary arteries in 3.

TABLE II Electrocardiographic and Angiographic Findings

	Patients	
	n	%
Resting ECG		
Normal	15	41
ST-T changes	22	59
ECG during spontaneous angina	27	73
S-T elevation	22	59
S-T depression	4	11
No change	1	3
Location of ischemia		
Anterior	17	46
Inferior	8	22
Both	1	2
Major arrhythmias during angina	10	27
Ventricular tachycardia/fibrillation	9	24
Complete heart block	2*	5
Syncope with arrhythmia	7	19
Coronary angiography	37	100
Normal coronary arteries	3	8
<50% lesions	32	86
50–70% lesions	2	5

* One patient had both ventricular tachycardia and complete heart block.
ECG = electrocardiogram.

TABLE III Results of Ergonovine and Exercise Testing

	Patients (n)
Positive ergonovine test	21*
At angiography	6
ECG alone	4
ECG + thallium-201 scan	15
Exercise test on no therapy	30
Positive test	13
S-T elevation	13
Site of ischemia during exercise	
Anterior	10
Inferior	1
Lateral	1
Anterior and inferior	1

* Four patients had 2 ergonovine tests.

Exercise testing: Thirty patients were exercised while they were off therapy (Table III). Thirteen had S-T elevation in at least 1 lead, and in 8 of these with an electrocardiogram during angina at rest the site of spontaneous and exercise ischemia was the same.

Treatment results (Table IV): All patients were commenced on verapamil, mean 260 mg/day in 3 or 4 divided doses. Twenty-four also received oral isosorbide dinitrate, mean 35 mg/day in 2 to 4 divided doses. After dose adjustment 19 patients became asymptomatic, and in 15 symptoms were satisfactorily controlled (1 to 4 attacks of angina per month). Two of these patients had angina after 2 and 4 months of therapy, respectively, in spite of a high dose of verapamil (520 and 800 mg daily) together with isosorbide (50 and 40 mg daily), but they responded to nifedipine and isosorbide. Three other patients did not respond to verapamil and isosorbide. Two of these, taking 320 and 480 mg of verapamil daily, respectively, continued to have ventricular tachycardia or fibrillation with spontaneous angina and were changed to nifedipine. One became asymptomatic; the other had 1 to 4 attacks of angina per month for 5 months and then became asymptomatic. The third patient failed to respond satisfactorily to verapamil or nifedipine, and continued to have an average of 8 episodes of angina per month while maintained on verapamil, 440 mg daily. The mean daily dose of nifedipine in the 4 patients who continued the drug was 58 mg (range 30 to 80), and 3 also took isosorbide 50 (range 20 to 80) mg daily.

TABLE IV Medical Therapy

	Patients (n)	Dose (mg/day)	
		Mean	Range
Initial therapy			
Verapamil	37	260	120–520
Additional isosorbide	24	35	20–50
Therapy at latest review			
Verapamil	27	314	120–600
Nifedipine	4	58	30–80
Additional isosorbide	16	41	20–80
No therapy	5	...	...
Nitroglycerin alone	1	...	...

TABLE V Results of Withdrawal From Therapy in 24 Patients

Supervised withdrawal	24 patients
Withdrawals (n)	26*
Recurrent angina <48 hours	10
Unsupervised withdrawal	5† patients
Withdrawals (n)	6‡
Recurrent angina <48 hours	2
Recurrent angina 2–4 months	4

* Two patients had 2 withdrawals.
† Two of the 5 also had supervised withdrawals.
‡ One patient had 2 withdrawals.

Twenty-seven patients continued on verapamil therapy for the whole period of follow-up; in 14 the dose was increased from a mean of 228 mg/day to 359 mg/day for symptomatic relief. Thirteen on a mean dose of 320 mg/day required no increase. The starting dose in the 14 patients who required an increase was significantly lower than in the 13 who did not (228 ± 88 versus 320 ± 71 mg/day, $p < 0.01$).

Of 12 patients who had a positive exercise test off therapy, a repeat test was negative on verapamil alone in 9 and became negative in the other 3 when nitrates were added to verapamil. In 3 a relationship was demonstrated between the plasma concentration of verapamil and the prevention of exercise spasm.[18] Twenty-four hour Holter recordings during therapy performed in 7 of the patients with a history of major arrhythmia showed no recurrence in any.

In 14 patients angina recurred as a result of a missed or late dose, or because of early timing of the last dose at night. This was most noticeable in the first month of therapy. Side effects were few and minor, and no patient required discontinuation of therapy. Three patients on verapamil complained of constipation, which responded to fecal softeners. One developed symptomatic hypotension late in the course of therapy, and this responded to reduced dosage. One patient on verapamil and 1 on nifedipine complained of fatigue, and 2 patients on nifedipine complained of headache.

Withdrawal from therapy (Table V): Twenty-four patients were admitted to the hospital for supervised withdrawal from therapy. Two patients had 2 withdrawals, making a total of 26 withdrawals in the 24 patients. Fifteen had no recurrence of angina or ischemic electrocardiographic changes. In 9 angina recurred within 48 hours, but in 2 only during an exercise test. In 7 of the 9 patients electrocardiographic changes accompanied angina. Five patients stopped treatment spontaneously, one of them on two occasions. Pain recurred in all 6 patients 24 hours to 4 months after withdrawal. Recurrence of angina on withdrawal was not influenced by the length of treatment or whether nitrates had been given in addition to verapamil. Only smoking was associated with recurrent angina. Fourteen of the 16 recurrences of angina were in smokers, whereas only 4 of the 16 patients without angina recurrence were smokers ($p < 0.02$).

When patients with recurrent angina recommenced therapy, they responded as before. One patient with recurrent angina declined further therapy. Six without angina did not recommence therapy, and 5 of these remained asymptomatic for a mean period of 10 months (range 3 to 18). The other had frequent angina 13 months after stopping therapy but responded when it was recommended.

Long-term follow-up (Table IV): At last review a mean of 21 months (range 1 to 61) after starting treatment, 27 patients were taking verapamil in a mean dose of 314 mg/day and 4 were taking nifedipine, 58 mg/day. Sixteen were taking additional isosorbide dinitrate, 41 mg/day. Twenty-one of the 31 treated patients were asymptomatic, 9 had only 1 to 4 episodes of angina monthly, and 1 had an average of 8 episodes of angina monthly. Six patients who had responded well to initial therapy were not on treatment at a mean of 28 months (range 4 to 47). Five remained asymptomatic and the 6th preferred to take nitroglycerin for angina. Of the 32 smokers on entry to the study, only 9 continued smoking.

Two patients were readmitted to the hospital for recurrent angina while on therapy. In one of these pindolol had been started for hypertension, and when it was discontinued the patient became asymptomatic. The other responded when verapamil was changed to nifedipine. Myocardial infraction or syncope did not occur during follow-up and there were no deaths.

Discussion

This study of a large group of patients with coronary artery spasm without severe coronary atherosclerotic obstruction shows that long-term therapy with verapamil or nifedipine is effective. Most patients responded well to verapamil and, if they did not, to nifedipine, emphasizing that when one calcium antagonist drug is ineffective at appropriate dosage a patient may respond to another. The therapeutic efficacy of verapamil is comparable to that in other reports.[10–14] No patient had to discontinue verapamil therapy because of side effects. As the period of follow-up is long, with high dosage in some patients, the lack of side effects from verapamil is an important finding; this has been reported previously.[19]

Associated isosorbide dinitrate therapy: Isosorbide dinitrate was given to almost 2/3 of patients in this study but was not effective by itself, as has been shown by others.[4,20] Most published studies on the management of coronary spasm have described the use of a single drug. In this study, some patients appeared to respond better to combined therapy with a calcium antagonist and isosorbide than to either drug alone. Similar findings were noted in another study.[14] As nitrates appear to act at a different site in vascular smooth muscle from calcium antagonists,[21] an additive or synergistic effect may explain the beneficial effect of combined therapy.

Effectiveness of verapamil: This was an open trial, so the response to therapy could be partly due to a placebo effect or the spontaneous cyclic remission of symptoms known to occur in this condition.[22] An effect from therapy was inferred because angina often occurred after a late or missed dose or after supervised withdrawal of verapamil, while an increase in the dosage often improved the clinical response. In another study the plasma concentration of verapamil was related to the prevention of exercise-induced coronary spasm, which also suggests a drug effect.[18] Double-blind cross-over trials confirm that verapamil is effective for coronary spasm.[11,23]

Role of beta-blocking drugs: Beta-blocking drugs were tried in 68% of our patients before diagnosis but did not reduce the frequency of angina. In 1 patient successfully treated with verapamil, angina recurred when a beta blocker was introduced for coexistent hypertension and abated when it was stopped. The lack of effect or aggravation of symptoms by beta blockers in patients with coronary spasm has been commented on by others,[2,3,12] and Robertson et al.[24] recently confirmed this in a double blind trial. Beta blockers should not be used in patients with coronary spasm.

Clinical features: The clinical findings in our patients are similar to those of previous reports.[2,20] Nocturnal angina was present in 85%, a history of Raynaud's disease or migraine in 25%, and mild hypertension in 43%. In contrast to previous reports nearly half of our patients complained of exercise-induced angina, suggesting that exertional spasm may occur frequently as has been reported elsewhere.[18] Most patients (86%) smoked cigarettes, but the mechanism whereby smoking may exacerbate symptoms is not known. When patients were admitted to the hospital acutely and stopped smoking anginal attacks continued, but those who continued to smoke long-term were more likely to develop angina when therapy was stopped. The cessation of smoking by a large number of patients may have beneficially influenced the long-term response to therapy, and is clearly part of the optimal treatment of these patients.

The clinical characteristics of patients with variant angina without significant coronary atherosclerosis are thought to differ from those of patients with severe coronary disease.[2] In the present study, the frequent finding of exertional angina and abnormal resting electrocardiogram, the large proportion of men, the preponderance of left coronary spasm, and the occasional occurrence of myocardial infarction emphasize that this difference may not be distinguished clinically. Coronary arteriography is mandatory for diagnosis and management.

Treatment withdrawal: Over half of the successfully treated patients did not develop angina when therapy was withdrawn at a mean of 15 months. Six remained off therapy and 5 were free from angina 10 months later. In several patients who did not develop angina on withdrawal treatment was recommenced because of previously documented malignant arrhythmias or because they desired to continue therapy. The reason for remission of symptoms in patients with coronary spasm is not known. As this condition is cyclical it is reasonable in asymptomatic patients who have

never had malignant arrhythmias or infarction to discontinue therapy under supervision after about 1 year.

Clinical implication: Patients with coronary artery spasm and minor coronary atherosclerosis have recurrent and disabling angina and are at risk from ventricular arrhythmias and myocardial infarction. Treatment with verapamil or nifedipine and nitrates is effective in the long-term and may prevent these life-threatening complications. Treatment can be withdrawn under supervision in certain patients without recurrence of angina.

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Pharmacokinetics of Verapamil: Experience With a Sustained Intravenous Infusion Regimen

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Disappearance kinetic characteristics of verapamil were determined in 9 patients after a single intravenous dose. From the pharmacokinetic variables determined, we designed an intravenous regimen to maintain a plasma verapamil concentration of 150 ng/ml consisting of (1) a loading bolus (10 mg over 2 minutes), followed by (2) a rapid loading infusion (0.375 mg/min) for 30 minutes, and finally (3) a maintenance infusion (0.125 mg/min). We tested this regimen in 7 patients for 2 to 12 hours, and found it to be safe and to produce stable prolongation of the P-R interval. Verapamil concentration was highest immediately after the bolus administration and was prevented from falling below 67 ng/ml by the rapid infusion. Maintenance concentration remained between 77 and 156 ng/ml for all patients, and averaged 122 ng/ml.

Transient and slight decreases in brachial blood pressure and sinus cycle length occurred coincident with the maximum verapamil concentration. Maximum P-R prolongation lagged behind peak plasma concentration but was sustained for the duration of the infusion. Prolongation of the P-R interval was not significantly different at the end of the infusion from that 90 minutes after the start of the regimen. No patient demonstrated significant side effects, arrhythmia, or clinically important hypotension. Although the specified regimen produced a final concentration averaging 125 ng/ml, it is predicted that infusion regimens producing other plasma concentrations can be similarly devised by changing the bolus, rapid loading infusion, and maintenance infusion doses in proportion to the desired final plasma concentration.

Verapamil is a prototypical slow channel blocker recently approved for intravenous use for treatment of supraventricular tachycardia. In controlled studies, intravenous verapamil has been shown effective in terminating paroxysmal supraventricular tachycardias[1–3] and in slowing the ventricular rate during atrial fibrillation.[1,3–6] In addition, verapamil may be useful in classic and variant angina pectoris, acute myocardial infarction, and hypertensive emergencies.[7,8]

Verapamil slows atrioventricular (AV) nodal conduction velocity (negative dromotropic effect) and prolongs AV nodal refractoriness.[9–15] These effects, which are brief after intravenous bolus verapamil,[3,4,6,11] no doubt contribute to the efficacy of verapamil in the therapy of supraventricular tachycardias. Under certain circumstances (such as control of ventricular rate in atrial fibrillation in a postoperative patient) a sustained negative dromotropic effect may be desirable. Oral verapamil has a more prolonged negative dromotropic action than intravenous bolus verapamil,[12,13] but its efficacy as an antiarrhythmic agent remains undetermined[14,15] and it was only recently approved for clinical use. The present study describes our experience with a concentration-maintaining regimen of intravenous verapamil that provides a sustained negative dromotropic action.

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Methods

Patients: Thirteen subjects (8 men and 5 women; mean age 40 years) were included in this study. Three of the 13 subjects were normal volunteers; the other 10 were patients who had paroxysmal supraventricular tachycardia but had sinus rhythm at the time of the study. No attempt was made to define the mechanism of the supraventricular tachycardia, although a delta wave indicative of the Wolff-Parkinson-White syndrome was intermittently recorded during sinus rhythm in 1 of the patients. Associated cardiac findings were mild hypertension (2 patients), mild aortic regurgitation (1 patient), and mitral valve prolapse (1 patient). Three patients had first degree AV block (P-R interval of 0.21, 0.21, and 0.24 second, respectively). No patient had congestive heart failure

and none had renal or hepatic dysfunction by clinical findings and serum chemistry values.

Digoxin was discontinued at least 1 week and all other cardioactive drugs at least 48 hours before study. All studies were conducted while the patients had normal sinus rhythm.

Administration of verapamil: Intravenous bolus injection: Nine subjects received 10 mg of verapamil (Isoptin,® Knoll Pharmaceutical, Whippany, New Jersey) in 4 ml of isotonic sterile saline solution delivered over 2 minutes by way of a running intravenous line through a 20 gauge Teflon® cannula inserted into a superficial arm vein. Serum for verapamil assay was obtained from a 20 gauge Teflon cannula positioned in the opposite forearm. Blood pressure and electrocardiographic intervals were recorded as each blood sample was drawn.

Intravenous sustained infusion: Plasma verapamil levels after bolus verapamil administration were fitted to a 2 compartment model and the pharmacokinetic variables were determined using a computer-assisted least-squares fitting of the log verapamil concentration versus time data. These pharmacokinetic variables were then used to devise a 3 stage concentration-maintaining regimen of intravenous verapamil by the method of separate exponentials[16]: *Step 1:* priming injection, verapamil 10 mg over 2 minutes; *Step 2:* rapid loading infusion, verapamil 0.375 mg/min for 30 minutes; *Step 3:* maintenance infusion, verapamil 0.125 mg/min. The rapid loading and maintenance infusions were obtained from a concentration of 0.375 mg verapamil per milliliter of sterile isotonic saline solution delivered at a rate of 60 and 20 ml/h, respectively, by a gravity fed controller (IVAC 230) through a 20 gauge Teflon cannula inserted into a superficial arm vein.

Plasma for verapamil assay was obtained from another 20 gauge cannula in the opposite arm. Blood pressure and electrocardiographic intervals were obtained as each blood sample was drawn.

Verapamil assay: Blood samples were placed in heparinized glass tubes and immediately centrifuged. The plasma was then separated, frozen, and stored at −20°C until assay. Plasma verapamil and norverapamil were measured using the high pressure liquid chromatographic assay described by Harapat and Kates.[17] The efficiency of the extraction technique was consistent and averaged 90% for verapamil and 76% for norverapamil. The assay was linear to at least 20 ng/ml, with a coefficient of variation of 7% for verapamil and 23% for norverapamil.

Electrocardiographic monitoring: A modified electrocardiographic lead II (left shoulder negative, cardiac apex positive) was displayed continuously using a Hewlett-Packard model 78100A and 78101A telemetry transmitter and receiver and a model 780-6A oscilloscope. Using an Elema Mingograf 8 channel recorder, an electrocardiographic rhythm strip was recorded at a paper speed of 100 mm/s at 15 minute intervals during the hour before the patients were given verapamil and as each blood sample was drawn. The P-R interval and cardiac cycle length were measured by hand and represent the mean of 7 to 10 consecutive heartbeats (rounded to the nearest millisecond) at each time interval. The electrocardiographic intervals for the control period were calculated as the mean of the intervals measured at the 5 different times during the 1 hour control period.

Blood pressures were determined by the cuff method immediately after each electrocardiographic rhythm strip was obtained.

Statistical methods: Changes in P-R interval, sinus cycle length, and blood pressure were tested for significance with the Wilcoxon signed rank order test or the sign test.

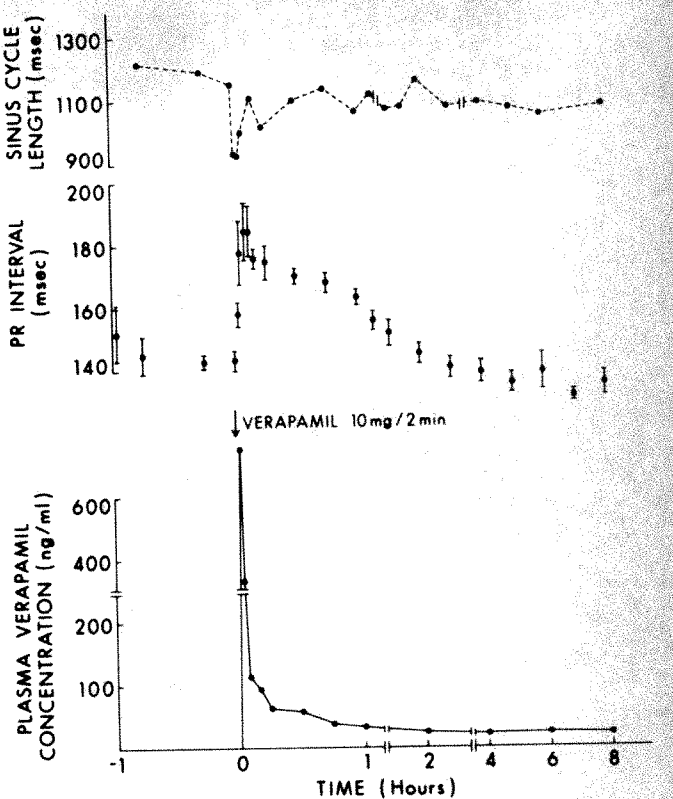

FIGURE 1. Patient 4. Plasma verapamil concentration, P-R interval, and sinus cycle length are shown versus time after administration of 10 mg of verapamil (given as a single intravenous dose over 2 minutes).

Results

Bolus Infusion

Administration of 10 mg verapamil as a single intravenous dose over 2 minutes resulted in peak plasma verapamil levels that occurred within 3 minutes after the start of drug administration (Fig. 1) and that varied widely (range 116 to 752 ng/ml; mean 426). The disappearance of verapamil fitted a 2 compartment model with a volume of distribution (central compartment) equal to 10.8 liters and a clearance rate equal to 47.6 liter/h. The kinetic variables that produced the best fit to the plasma concentration-time data are shown in Table I.

Blood pressure and sinus cycle length decreased slightly but significantly immediately after the end of verapamil administration but then returned to normal. Mean systolic blood pressure decreased 17 ± 13 mm Hg from a control value of 126 mm Hg. Mean sinus cycle length decreased from a control value of 1,003 ± 178 ms (heart rate 60 beats/min) to 801 ± 140 ms (heart rate 75 beats/min). No patient developed sinus tachycardia, although 1 patient developed an accelerated junctional rhythm (cycle length 566 ms). No patient developed AV nodal block, symptomatic hypotension, or side effects. Prolongation of the P-R interval was noted at 2 minutes, but maximum prolongation (125% of control P-R interval) lagged behind peak plasma verapamil concentration and occurred 5 to 30 minutes after the start of the infusion in all 9 patients (Fig. 1). The pro-

TABLE I Pharmacokinetic Variables Derived From a Single Intravenous Dose of 10 mg of Verapamil in 9 Subjects

Patient	Age (yr) & Sex	Weight (kg)	A_0 (ng/ml)	α (h^{-1})	B_0 (ng/ml)	β (h^{-1})
1	28M	96	132	−19.5	49.6	−0.30
2	46F	68	764	−58.2	89.8	−0.34
3	65M	57	1532	−41.8	42.5	−0.14
4	50F	66	1530	−58.3	77.5	−0.47
5	28M	64	435	−32.4	55.4	−0.63
6	58M	84	1,280	−48.6	68.3	−0.36
7	26F	50	749	−48.5	130.8	−0.48
8	44F	65	218	−30.6	48.6	−0.27
9	61M	83	1,052	−28.3	67.1	−0.34
Mean	...	...	854.7	−40.7	70.0	−0.37
SD	...	...	±531	±13.8	±27.4	±0.14

V_d = Dose/(A_0 + B_0) = 10.8 liters
Cl = Dose/AUC, where AUC = $A_0/\alpha + B_0/\beta$ = 47.6 liters/h.

α = rate constant for the early distribution phase; A_0 = zero-time intercept of the α-phase; AUC = total area under the plasma concentration-time curve; β = rate constant for the terminal phase; B_0 = zero-time intercept of the β-phase, where the decline in measured plasma concentration (C_t) after a single intravenous injection is described by the expression $C_t = A_0e^{-\alpha t} + B_0e^{-\beta t}$; Cl = total clearance of verapamil; SD = standard deviation; V_d = volume of distribution (central compartment).

longation of the P-R interval began decreasing 30 minutes after verapamil was administered. The P-R interval 90 minutes after intravenous administration of verapamil differed from the control value by less than 5%.

Sustained Infusion

From the average kinetic variables calculated, the method of separate exponentials was used to simulate various infusion regimens. The final regimen selected was designed to rapidly achieve and maintain a plasma verapamil concentration of approximately 150 ng/ml. The decrease in concentration (because of rapid drug distribution) before steady state is reached (Fig. 2, bolus plus maintenance infusion) was prevented by a rapid loading infusion. The rapid infusion was chosen so that the verapamil concentration remained within the arbitrary limits of 100 and 175 ng/ml during the loading infusion. The final loading infusion selected was a multiple of the maintenance infusion to simplify delivery. Simulations of the plasma concentration for the bolus alone, the bolus plus the maintenance infusion, and the sum of the bolus, maintenance, and rapid loading infusions together are shown in Figure 2. This regimen has been tested in 1 patient each for 2 and 4 hours, in 2 patients for 6 hours, and in 3 patients for 12 hours. Mean and extreme values of plasma verapamil concentration are shown in Figure 3.

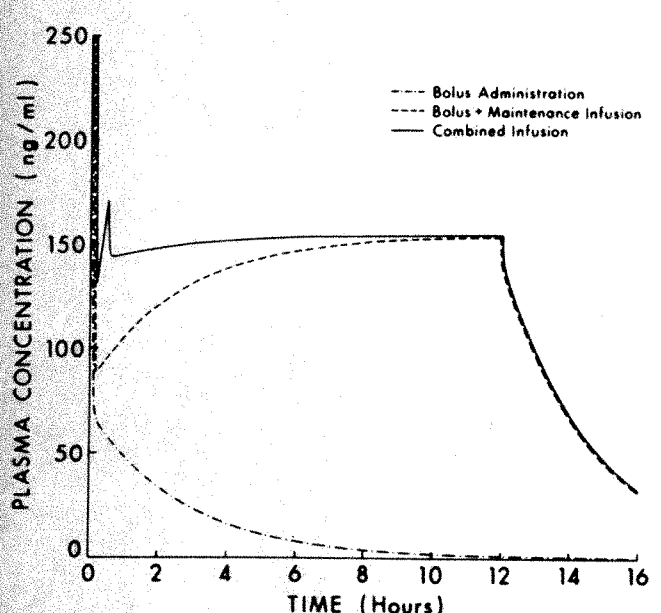

FIGURE 2. Simulations (utilizing the method of separate exponentials) of plasma verapamil concentration versus time are presented for the bolus (10 mg over 2 minutes) alone, the bolus plus the maintenance (0.125 mg/min) infusion, and the sum of the bolus, maintenance, and rapid loading (0.375 mg/min for 30 minutes) infusions.

Plasma verapamil concentration: Peak verapamil concentrations were comparable to those obtained during bolus administration (Table II). Plasma verapamil concentrations reached their nadir 5 to 10 minutes after the start of verapamil administration but did not fall below 67 ng/ml in any patient and averaged 133 ± 45 ng/ml. At the end of the rapid loading infusion, the mean plasma verapamil concentration for the 7 patients was 157 ng/ml (range 114 to 227). This contrasts with mean plasma verapamil concentrations of 81 and 58 ng/ml, respectively, 10 and 30 minutes after a single bolus administration.

Plasma verapamil concentration during the maintenance infusion remained relatively constant for each patient and ranged from 77 to 174 ng/ml (mean 122 ± 21) for all patients. The variation in concentration did not appear to be related to differences in patient weight. There was no apparent increase in plasma verapamil concentration during the infusion.

Norverapamil concentration: Norverapamil, the n-demethylated metabolite of verapamil, reached measurable plasma levels 30 to 60 minutes after the start of verapamil administration in all patients. Mean norverapamil concentration at the end of the infusion was 33 ± 7 ng/ml (range 19 to 39). Maximum norverapamil levels occurred within 1 hour after terminating the infusion and ranged between 30 and 41 ng/ml for all patients. The 3 individuals who received 12 hour infu-

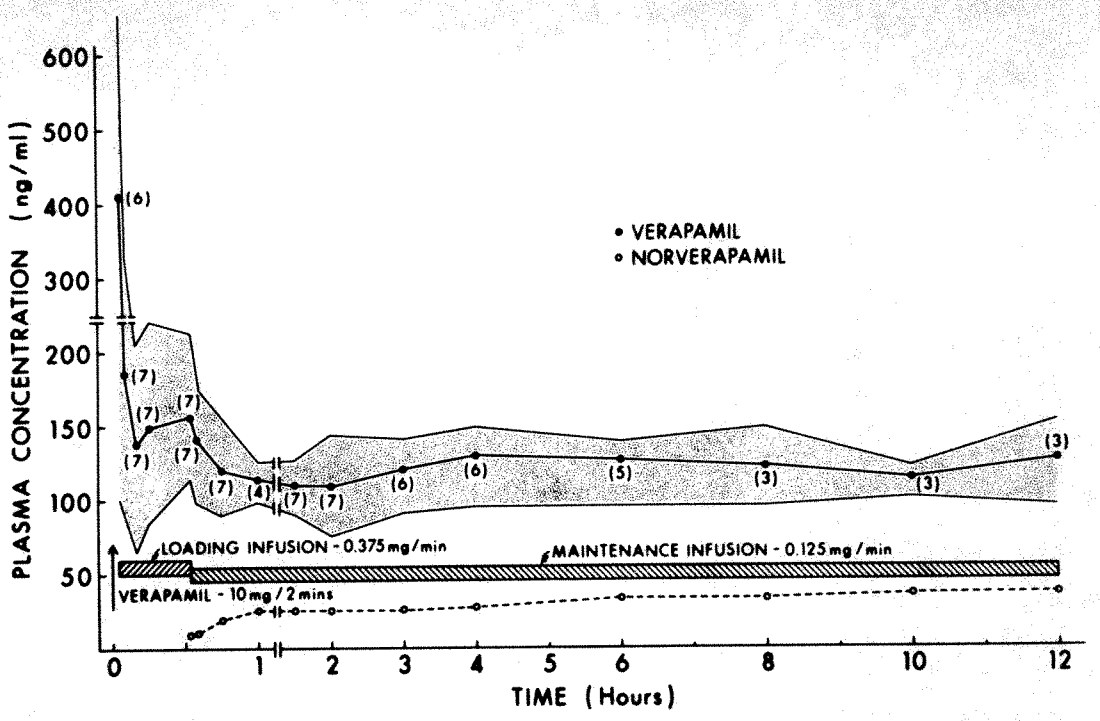

FIGURE 3. Mean and range of plasma verapamil concentration and mean norverapamil concentration are shown for the 7 patients who received the concentration-maintaining intravenous regimen. The number of patients for whom data are available at each time is shown in parentheses.

sions achieved a norverapamil level of 40, 41, and 36 ng/ml, respectively.

Blood pressure and heart rate: Brachial blood pressure and sinus cycle length decreased slightly in the first 3 minutes corresponding to the peak plasma verapamil concentration, but there was no sustained decrease in either. Mean systolic blood pressure decreased 10 ± 6 mm Hg from a control value of 118 mm Hg. Mean sinus cycle length decreased from 998 ± 33 ms (heart rate 60 beats/min) to 800 ± 94 ms (heart rate 75 beats/min). There was no significant decrease in blood pressure or cycle length at the second peak in plasma verapamil concentration (157 ng/ml) at the end of the rapid loading infusion.

P-R interval: The P-R interval was prolonged in all patients at 2 minutes (Fig. 4). Maximum negative dromotropic effect (138 ± 11% of control P-R interval) occurred between 5 and 45 minutes. Unlike the transient changes in blood pressure and sinus cycle length, P-R prolongation was sustained over the duration of the infusion (averaging 127% of control P-R interval) without apparent diminution and then slowly returned to normal in the 4 hours after termination of the infusion. Although first degree AV nodal block was common, no patient developed Wenckebach conduction or AV dissociation during the infusion.

Side effects: No significant side effects were noted during the sustained infusion of verapamil. One patient developed a mild headache 3 hours after the start of the infusion. The other six patients were without symptoms. No clinically significant hypotension, bradycardia, or arrhythmia occurred in any patient.

Discussion

We have described a concentration-maintaining method of administering verapamil. This 3 component regimen has the advantages of (1) rapid achievement

TABLE II Effects of Sustained Intravenous Verapamil Infusion in 7 Patients*

	Verapamil Concentration (ng/ml)		P-R Interval (ms)			Heart Rate (beats/min)			Blood Pressure (mm Hg)		
Subject	Peak	Steady State*	Control	Maximum	Steady State†	Control	Maximum	Steady State†	Control	Minimum	Steady State†
6	530	148 (116–148)	173	222	196 (192–204)	72	79	66 (58–67)	120/80	114/74	120/70
8	420	92 (92–98)	197	282	256 (256–290)	53	70	57 (56–58)	96/64	84/56	94/60
9	815	130 (105–138)	240	344	304 (284–331)	55	63	54 (47–56)	146/86	130/70	144/84
10	138	126 (116–132)	178	211	202 (194–204)	81	89	81 (79–85)	106/72	104/60	104/60
11	757	134 (117–147)	127	186	155 (153–172)	59	84	58 (58–68)	112/76	106/70	116/82
12	655	152 (111–152)	163	208	198 (198–204)	58	74	52 (52–65)	118/82	104/72	118/78
13	102	95 (77–101)	175	240	198 (189–235)	54	70	62 (54–69)	128/84	114/76	132/86

* Subjects 11 to 13 were normal volunteers; all others had paroxysmal supraventricular tachycardia.
† Steady state values represent observations at the end of the maintenance infusion. Values in parentheses represent the range of observations from the first hour to the end of the infusion.

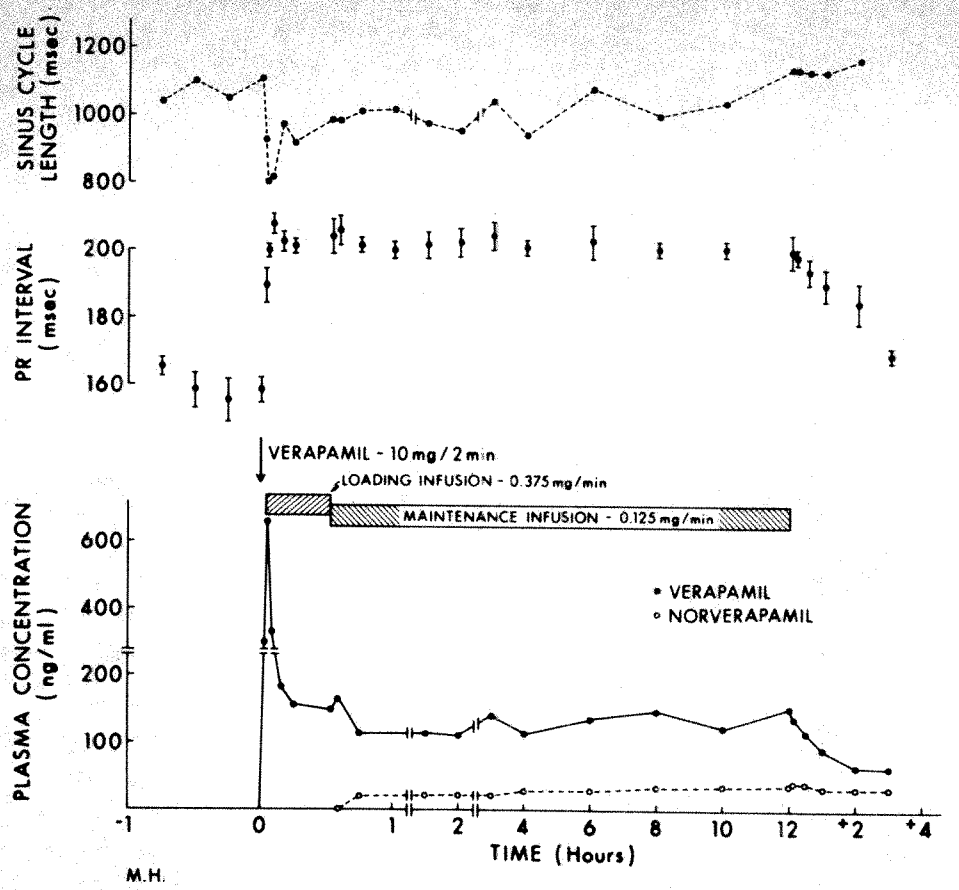

FIGURE 4. Patient 12. Plasma verapamil concentration, P-R interval, and sinus cycle length are shown for a patient who received the dose-maintaining regimen for 12 hours.

of therapeutic level, (2) elimination of a "dip" in concentration by the rapid loading infusion, (3) maintenance of steady state concentrations without significant accumulation (at least up to 12 hours), and (4) ease of administration. This regimen was tested in 7 patients and was found to be safe and to produce stable P-R interval prolongation for up to 12 hours.

Pharmacokinetics of verapamil: The final regimen selected and tested was based on pharmacokinetic variables determined after a single intravenous injection of verapamil. We elected to model the data from the 9 subjects who received a single injection to a 2 compartment model. This is in agreement with the observations of Dominic et al.,[18] who reported very similar values for the distribution and elimination phase half-lives as well as plasma clearance. Recently, Kates et al.[19] studied the disposition kinetic features of verapamil in patients with chronic atrial fibrillation and obtained similar values for clearance (13.3 ± 7.7 ml/min/kg) and for the volume of the central compartment (28.6 ± 24 liters). However, their pharmacokinetic data were interpreted as showing 3 exponential kinetics. This difference is probably related to the longer sampling time of Kates et al. Our data might similarly be solved by curves described by 3 exponents with a curve-fitting error comparable to the 2 exponent solution. We solved for 2 exponent terms to simplify the simulations by the method of separate exponentials. The success of our final regimen justifies this simplification.

Optimal plasma concentration: We constructed our infusion regimen to produce a plasma verapamil concentration of 150 ng/ml because this level has been shown to cause substantial slowing of AV nodal conduction.[11,20] Schwartz et al.[21] have shown that this plasma drug level produces stable slowing of the ventricular rate in patients with atrial fibrillation. However, other plasma concentrations are easily attainable. The method of separate exponentials predicts that other concentrations can be similarly achieved by changing the bolus, rapid loading infusion, and maintenance infusion doses by an amount in proportion to the desired final concentration. Thus, a final verapamil concentration of about 60 to 75 ng/ml can be achieved by a 5 mg bolus (10 mg × 0.5) over 2 minutes, a rapid loading infusion of 0.188 mg/min (0.375 mg × 0.5) for 30 minutes, and a maintenance infusion of 0.06 mg/min (0.125 × 0.5).

Verapamil metabolism and excretion: Verapamil undergoes hepatic metabolism before renal excretion. Only 3 to 4% of an oral dose is excreted as unmetabolized drug.[22] The major metabolic step involves N-deakylation with further metabolism by O-demethylation and subsequent conjugation. Norverapamil and other metabolites of verapamil may reach levels in the

plasma similar to or higher than those of verapamil after oral administration. In the present study, norverapamil was seen to accumulate during sustained intravenous infusion. However, norverapamil and the other major N-demethylated metabolites have insignificant effects on the AV node and hemodynamic effects significantly smaller than that of the parent drug.[23] Thus, there is no evidence that accumulation of metabolites during prolonged intravenous infusion would have untoward electrophysiologic or hemodynamic effects, although we have not directly evaluated this question. Verapamil clearance is decreased in patients with hepatic disease,[24] and the cautious use of verapamil by any route is appropriate in such patients or with the combined use of verapamil and cimetidine, which decreases hepatic blood flow.

Clinical implications: The benefit of verapamil in the therapy of supraventricular arrhythmias is related to its negative dromotropic effect on the AV node. The effect of a single intravenous dose of verapamil is transient and begins to decrease within 30 minutes, as shown in this and other[3,11,18] reports. This time course of dromotropic effect is similar to the effects of verapamil in slowing the ventricular rate in atrial fibrillation.[4,6,15] Our infusion regimen should be useful when a longer effect is desirable (for example, in the treatment of supraventricular tachycardia after cardiac surgery or myocardial infarction).

The blocking effect of verapamil on AV nodal conduction is due to its effect on the calcium-mediated slow response, an action unlike that of other antiarrhythmic agents. Thus, sustained intravenous verapamil infusion may be useful alone, or before or in combination with digoxin therapy, for the acute control of ventricular response where cardioversion is not indicated or not effective. Verapamil may have advantages over propranolol because it does not alter airway resistance and the negative inotropic action of verapamil is partly offset by a decrease in afterload. However, verapamil may produce a greater degree of hypotension in patients with atrial fibrillation than in patients with sinus rhythm[6] and may be deleterious in patients with severely reduced left ventricular function or with elevated left ventricular filling pressure.[25] Because of limited experience, sustained intravenous verapamil should be administered with caution in patients with left ventricular dysfunction. The concomitant use of intravenous verapamil and beta blockers is relatively contraindicated because of the reports of serious adverse reactions. Finally, this type of infusion may also be applicable in the treatment of hypertension, unstable angina, or variant angina because verapamil also causes dilatation of the coronary and systemic arteries. However, the hemodynamic effects of a sustained infusion of verapamil in these conditions has not yet been assessed.

Safety: The concentration-maintaining regimen that we designed to provide a verapamil plasma concentration of approximately 150 ng/ml can produce a sustained negative dromotropic effect comparable to the maximal effect seen after a single dose of 10 mg verapamil. During infusions up to 12 hours, no notable diminution of negative dromotropic effect was apparent. There was no evidence of significant tachyphalaxis or inhibition of the action of verapamil by metabolic alteration of the molecule. Moreover, the sustained plasma concentration was not associated with significant or sustained changes in blood pressure or sinus cycle length. We conclude that the described regimen will produce stable verapamil levels, sustained AV nodal slowing, and no significant toxicity.

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Variability of Response to Beta Receptor Blockade for Angina Pectoris in Clinical Trials: A Study of Pindolol

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In a randomized, controlled study we found a significant decrease in pressure-rate (double) product and an improvement in exercise tolerance in patients with angina pectoris treated with pindolol. However, when patients were observed in a long-term double-blind crossover study, pindolol treatment did not produce a significant improvement in angina pectoris or exercise tolerance over placebo. Patients treated with placebo had a gradual improvement in exercise tolerance, possibly because of the training effect of multiple treadmill tests and increased daily walking. The individual patient response to pindolol varied, with some patients showing clinical improvement and decreased double product with exercise and some having no clinical improvement despite a similar decrease in double product. Angina occurred at a lower double product with exercise, suggesting that beta receptor blockade adversely affected other variables of myocardial oxygen demand or decreased coronary blood supply. This study illustrates the difficulties with patient variability and study design that are encountered in studies of beta blocker agents for angina pectoris.

Pindolol is a nonselective beta receptor blocker that is 4 to 5 times as potent as propranolol on a milligram per milligram basis. Pindolol has intrinsic sympathomimetic activity and alters resting heart rate, left ventricular size,[1] and airway resistance[2] less than propranolol. We have studied the effects of pindolol on the frequency of angina attacks and on treadmill exercise tolerance in patients with stable angina pectoris. Previous studies using various types of protocols have produced conflicting results. To assess factors which may explain variability in results, we evaluated individual patient response and studied the same patients in a short-term comparison with placebo in parallel groups and in a longer double-blind crossover study.

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Methods

Study patients: Fourteen patients with stable angina pectoris were studied. Two patients did not complete the study and are not included in the analysis. One patient discontinued the study because there were "too many treadmill tests." One patient was dropped from the study in the baseline period because of nonreproducible treadmill tolerance, ranging from 2 to 8 minutes on the same day with no obvious explanation. The average age was 52 years (range 35 to 68). There were 11 men and 1 woman. All patients had coronary artery disease documented by coronary arteriography with luminal stenosis of at least 70% in 1 or more coronary vessels. Each patient had stable angina pectoris for at least 3 months and had a positive treadmill test with a minimum of 1 mm of S-T segment depression accompanied by typical angina pectoris. No patient had hypertension, congestive heart failure, valvular heart disease, bradycardia less than 50 beats/min, or obstructive lung disease requiring treatment with bronchodilators, and none had had coronary bypass surgery or myocardial infarction in the previous 3 months. While no patient received other beta blocker agents, long-acting nitrates, or antihypertensive medication, any other medications the patients were chronically taking were not changed during the study period.

Study protocol (Fig. 1): The study protocol was a 15 week double-blind, randomized study in a crossover design. Weeks

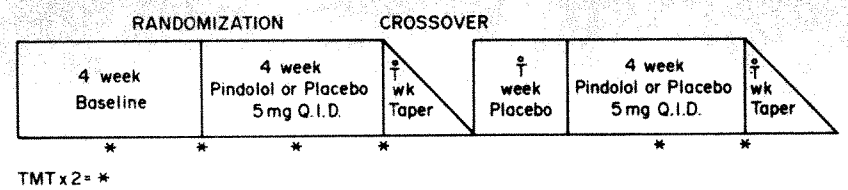

FIGURE 1. Diagram of study protocol. Treadmill tests (TMT) were done in duplicate 15 to 60 minutes apart at indicated intervals. wk = week.

1 to 4 were a baseline period in which the patients received placebo medication in a single-blind fashion. They were then randomized to sequence group 1 to 2. Sequence group 1 received placebo 4 times a day from weeks 5 through 8 and 5 mg of pindolol 4 times a day from weeks 11 to 14 in a double-blind design. Sequence group 2 received the treatments in reverse order. Weeks 9 and 15 were tapering off periods and week 10 was a crossover single-blind placebo period.

Variables evaluated: Each patient kept an angina diary and recorded the number and character of episodes of angina pectoris and the number of nitroglycerin tablets used. Daily activity was estimated by a pedometer recording the miles walked. At the end of weeks 2 and 4 in the baseline period and at the end of weeks 6, 8, 12, and 14 in the randomization periods, treadmill tests were done in duplicate 15 to 60 minutes apart. The treadmill tests were done in the postabsorptive state at the same time of day each visit 2 to 3 hours after a dose of study medication.

Treadmill tests were done according to the following protocol: Stage I, 1 mile/h at 0° elevation; stage II, 1 mile/h at 10° elevation; stage III, 1.5 miles/h at 10° elevation; and stage IV, 2 miles/h at 12° elevation. Each stage was continued for 3 minutes.

An electrocardiogram with 3 modified Frank vector leads and blood pressure were taken at rest and at the end of each stage and at the end-point of exercise. The electrocardiogram was monitored continuously by oscilloscope. Exercise was carried to the end-point of the patient's typical angina on each test, and the patients were asked to exercise to the same symptomatic point on each test. Each patient had a positive electrocardiographic response as defined by at least 1 mm flat or downsloping S-T depression for at least 0.08 second duration. The heart rate and systolic blood pressure product, an index of myocardial oxygen demand,[3] was calculated at rest and at the exact end-point of exercise.

Every 2 weeks a detailed cardiac history and physical examination were performed. Electrocardiogram, chest x-ray film, complete blood count, urinalysis, and routine blood chemistry determinations were done at entry and at the end of weeks 4, 9, and 15. Pindolol blood levels were drawn between the duplicate treadmill tests and analyzed by Sandoz Laboratories.

Statistical analysis: In comparing the 2 study groups, differences were calculated using an analysis of variance for a 2 period crossover study design. When evaluating a change from baseline for a single group, one-way analysis of covariance was used. Differences in baseline characteristics of groups A (good response) and B (poor response) were evaluated by the *t* test and chi-square test.

Results

Pindolol versus placebo: Table I summarizes the effects of pindolol on the clinical and exercise variables studied during the crossover study. The number of angina pectoris episodes and nitroglycerin tablets used per week and the amount of S-T depression at peak exercise on the treadmill were decreased more by pindolol than by placebo, but the differences were not statistically significant. The patients had a similar degree of improvement in exercise tolerance on the treadmill with both pindolol and placebo. The only difference between pindolol and placebo that was statistically significant was the reduction of rate-pressure product on the treadmill at peak exercise.

Types of response to pindolol: Figures 2 to 6 demonstrate the 3 types of response to pindolol shown by the individual patients. Four patients (Group A) had a good hemodynamic and clinical response to pindolol as demonstrated by Patient 14 in Figure 2. This group had a marked reduction in rate-pressure product at peak exercise and increased treadmill exercise tolerance over placebo (Fig. 3). Six patients (Group B) (Fig. 4) did not have improved exercise tolerance despite a reduction in rate-pressure product on exercise similar to that seen in Group A (illustrated by Patient 9 in Fig. 5). Two patients showed no difference in rate-pressure product at the end-point of exercise or in exercise tolerance between placebo and pindolol (Fig. 6).

Evaluation of baseline clinical factors in Group A (good response) and Group B patients showed no difference in the incidence of previous myocardial infarction, frequency of angina pectoris, baseline blood pressure, cardiothoracic ratio on chest x-ray, or whether they had placebo or pindolol in the first study period. However, Group A patients were older (59 years with

TABLE I Effects of Pindolol on Clinical and Exercise Variables

	Baseline	% Δ on Placebo	% Δ on Pindolol	% Differences in Pindolol and Placebo
AP/wk	5.2	−18	−32	14
TNG/wk	4.9	+6	−8	14
DP on TM	19,443	−0.5	−24	23.5*
Ex Tol on TM (s)	252.8	+11	+13	2
S-T dep on TM (mm)	1.9	−8	−14	6

* $p < 0.01$.

AP/wk = episodes of angina pectoris per week; DP on TM = double-product on treadmill test at end-point; Ex Tol on TM = duration of exercise tolerance on treadmill test; ST dep on TM = amount of S-T depression at end-point of exercise; TNG/wk = number of nitroglycerin tablets used per week; % Δ = percent change.

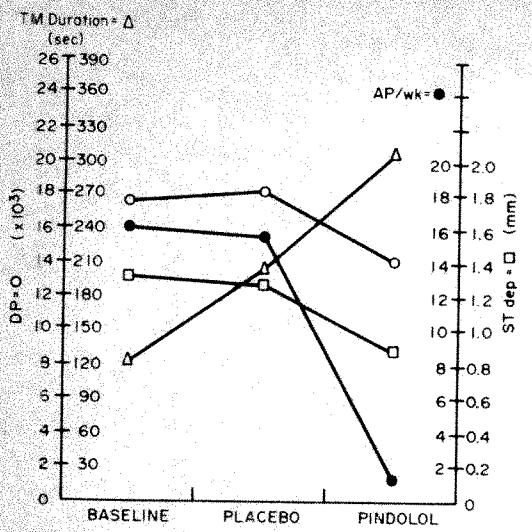

FIGURE 2. Patient 14. Results of measured variables at baseline, and in placebo and pindolol study periods. AP/wk = episodes of angina pectoris per week; DP = double-product at end-point of exercise; ST dep = S-T depression on electrocardiogram at end-point of exercise; TM Duration = treadmill duration (in seconds).

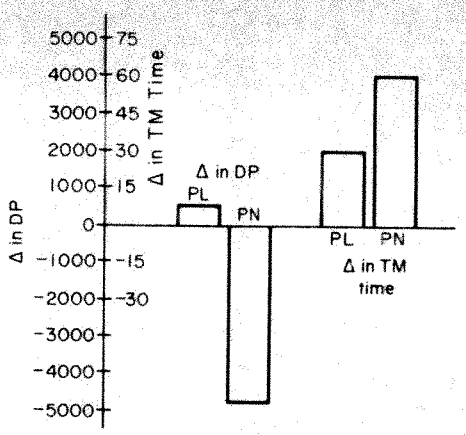

FIGURE 3. Improvement in double-product at peak exercise and exercise tolerance on the treadmill in Group A (4 patients with good clinical and treadmill response to pindolol). Δ in DP = change in double-product at the end-point of exercise from baseline; PL = placebo; PN = pindolol; Δ in TM time = change in exercise tolerance on treadmill from baseline (in seconds).

range of 64 to 67, versus 49 years with range of 40 to 61; $p < 0.02$), developed angina earlier on the baseline treadmill test (157.5 seconds, with range of 120 to 240, versus 250 seconds, with range of 195 to 390; $p < 0.05$), and had a longer duration of symptomatic ischemic heart disease (107 months, with range 56 to 240, versus 49 months, with range of 12 to 120; $p = 0.05$ to 0.10). In addition, Group A patients had a lower baseline standing heart rate (74 beats/min, with range of 60 to 85, versus 93 beats/min with range of 75 to 108; $p < 0.02$) and a slightly lower baseline supine heart rate (66 beats/min, with range of 52 to 75, versus 77 beats/min, with range of 64 to 90; $p = 0.05$ to 0.10). Angiography had been performed at varying periods of time before the study (3 months to 6 years), and the data on left ventricular function and severity of coronary disease were not considered valid for this analysis.

Sequence group 1 versus sequence group 2: Serial exercise tolerance was evaluated in the patients who were on placebo for the first 8 weeks of the study (4 weeks in the baseline period and 4 weeks in the first study period on placebo). Figure 7 shows a steady increase in exercise tolerance over the 8 week period while the patients were on placebo only. An alternate method of assessing the response to pindolol is to compare the baseline variables with those measured during the first

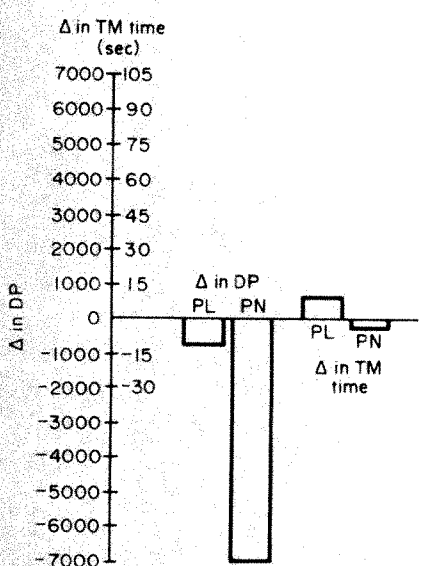

FIGURE 4. Change from baseline in double-product at the end-point of exercise and exercise tolerance on the treadmill in Group B (6 patients with a poor clinical and treadmill response despite reductions in double-product). Abbreviations as in Figure 3.

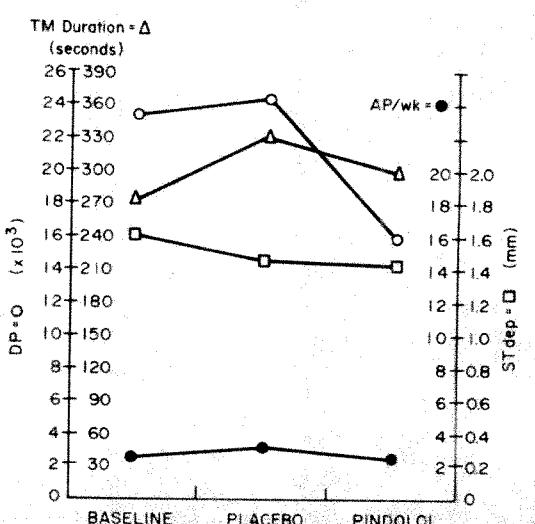

FIGURE 5. Patient 9. Results of measured variables at baseline, and in placebo and pindolol study periods. Abbreviations as in Figure 2.

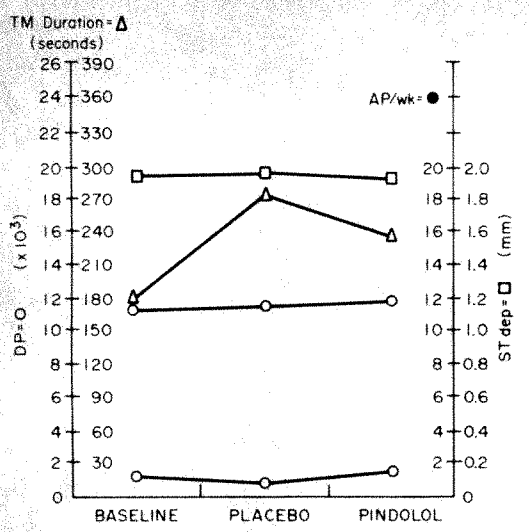

FIGURE 6. Patient 7. Results of measured variables at baseline, and in placebo and pindolol study periods. Abbreviations as in Figure 2.

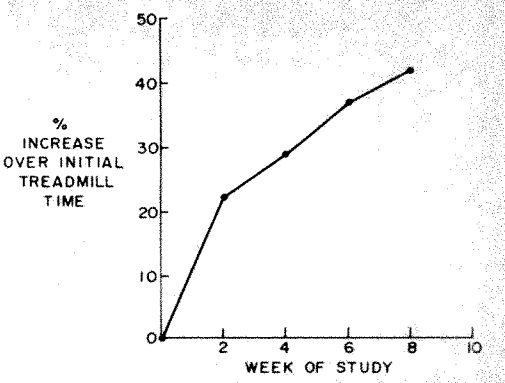

FIGURE 7. Sequence group 1. Percent increase in exercise tolerance on treadmill test in patients who were on placebo for first 8 weeks of study (4 weeks of stabilization and 4 weeks in first study period on placebo).

study period with each patient serving as his own control. There was no significant change in rate-pressure product at the end-point of exercise in the placebo period, but patients on pindolol had a 25% reduction ($p < 0.05$) in the double-product (Fig. 8). Similarly, there was a 16% increase ($p < 0.05$) in treadmill exercise tolerance in the patients on pindolol in the first study period (Fig. 9).

Pindolol blood level: The mean pindolol blood level was 22.3 ng/ml (range 5 to 37.5). Patients with a good clinical response (Group A) had blood levels (mean 23.1 ng/ml) that were similar to those of patients with poor clinical response (mean 24.6 ng/ml). One of the 2 patients who showed no reduction in double-product at peak exercise had the lowest drug level.

Daily walking: During the single-blind placebo stabilization period the patients walked an average of 1.31 miles/day, on pindolol 1.25 miles/day, and in the double-blind placebo period 1.47 miles/day, values which are not significantly different. During the baseline 4 week period patients walked an average of 1.31 miles/day, and during the last study period they walked an average of 1.46 miles/day.

Side effects: Pindolol did not produce any hematologic, hepatic, renal, or metabolic abnormality as evaluated by serial complete blood counts and routine blood chemistry values. Evaluation for multiple side effects revealed that only fatigue (5 patients versus 1 patient) and insomnia (4 patients versus 2 patients) occurred more often on pindolol than placebo.

Discussion

Comparison with previous studies (Table II): In previous studies the effect of pindolol on angina pectoris has been assessed using various protocols; 42 to 85% of patients had decreased angina pectoris on pindolol and there was 12 to 21% improvement in exercise tolerance on pindolol. In general, a greater improvement with the drug was seen in uncontrolled studies and in those in

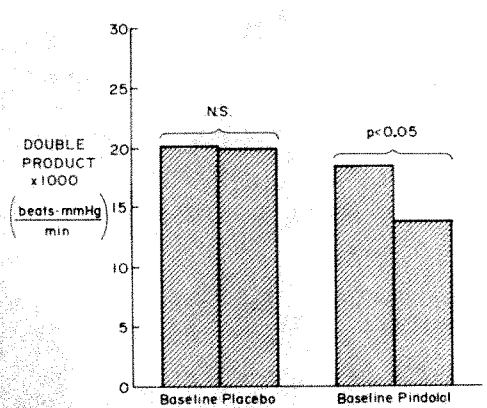

FIGURE 8. Change in double-product at the end-point of exercise in the first study period (placebo or pindolol) compared with baseline. N.S. = not significant.

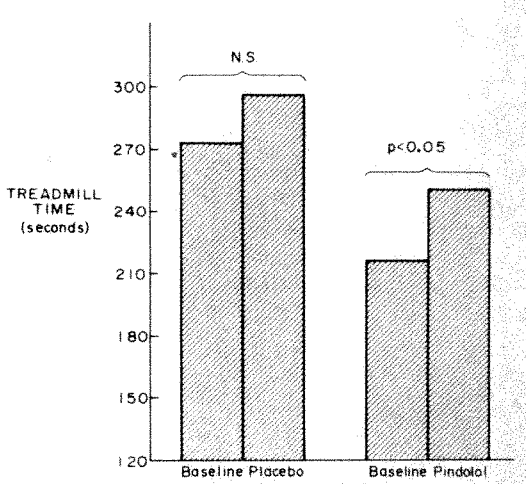

FIGURE 9. Change in exercise tolerance on the treadmill in the first study period (placebo or pindolol) compared with baseline. N.S. = not significant.

TABLE II Previous Studies of Pindolol in Angina Pectoris

Study	Patients (n)	Study Design	Duration of Study (wk)	Daily Dose (mg)	% Patients With Decreased Angina	% Reduction in Angina Pectoris	% Improvement in Exercise Tolerance
Present study	12	A	15	20	42	32	13
Arstila et al.[4]	20	B	24	20	50	23	12
Frishman et al.[1]	23	C	12	40	NR	53	21
Thorpe[5]	16	A	10	20	75	NR	NR
Nair[6]	30	D	6	10	80	NR	NR
Sainani and Mukherjee[7]	25	D	6	10	72	*	†
Arvanis and Michaelides[8]	48	E	4–40	7.5–40	85	NR	NR
Saner[9]	14	E	NR	15	71	NR	NR

* Fifty-six % of patients had a greater than 25% reduction in angina pectoris.
† Ten of 25 patients improved 50%; 7 of 25 patients showed no change or had decreased exercise tolerance.
A = double-blind crossover comparison with placebo; B = double-blind crossover comparison with propranolol and placebo; C = double-blind comparison with propranolol; D = double-blind comparison with placebo; E = not controlled; NR = not reported.

which the period of observation was shorter. Our results are remarkably similar to those of Arstila et al.,[4] and both studies used a double-blind crossover protocol with repeated evaluation of exercise tolerance. Slightly greater improvements in exercise tolerance by pindolol was demonstrated by Frishman et al.,[1] using a higher dose than that used by others. The inability to demonstrate an important clinical improvement in these studies probably is not related to the particular beta blocker agent being used since propranolol and pindolol were compared and produced quite similar results in 2 of the studies.[1,4]

Role of protocol design and interpretation of patient responses: Our study emphasizes the complexity involved in protocol design and interpretation of responses to beta blocker agents in stable angina pectoris. We can identify several factors that could be responsible for the varying responses of the patients in our study and that we assume may be confounding factors in any study similarly designed (Table III). The variable response to a given dosage and blood level of beta blocker drug in individual patients may reflect differences in sympathetic nervous system output at rest and with exercise or differences in individual absorption and metabolism. Ideally, the dosage for optimal beta receptor blockade should be titrated for each individual patient, using response to isoproterenol infusion or percentage reduction in heart rate with exercise as the end-point. However, this is virtually impossible to do in a placebo-controlled double-blind crossover study.

TABLE III Difficulties in Evaluating Beta-Blocking Agents in Angina Pectoris

I. Variables of study drug pharmacokinetics
  A. Variable response to same blood level
    1. Intrinsic sympathetic tone
    2. Receptor sensitivity to drug
  B. Variable blood level for same dose
    1. Absorption
    2. Distribution and metabolism
II. Hemodynamic variables in patients
  A. Left ventricular volume and pressure
  B. Coronary vasoreactivity
  C. Coronary flow distribution
III. Placebo effect: more prominent in short-term study with subjective evaluation
IV. Training effect: more prominent long-term study with exercise evaluation
V. Spontaneous change in underlying disease

Exercise tolerance after pindolol: The desired effect of beta blocker agents in ischemic heart disease is to reduce the myocardial oxygen consumption by decreasing heart rate and blood pressure, particularly with exercise. Pindolol produced a significant reduction in rate-pressure product on exercise in our study, and this was noted in 10 of 12 patients. Despite this favorable effect, 6 of the 10 patients (Group B) did not have an increase in exercise tolerance before developing angina. Our 4 patients with a good response (Group A) were older, had a longer duration of symptoms and had more limiting angina as demonstrated by poor treadmill exercise tolerance at baseline. Perhaps a similar degree of beta blockade produced a greater clinical response in such patients. The 6 patients with a poor response had a higher resting heart rate at baseline. This could have indicated higher baseline sympathetic tone and might require a higher dose of beta blocker agent.

The occurrence of angina at a lower rate-pressure product on a beta blocker agent was also noted by Arstila et al.,[4] who postulated that this could be due to an increase in myocardial oxygen consumption through increased left ventricular volume and wall stress, or a decreased supply either in overall coronary flow or a change in distribution of flow. Frishman et al.[1] showed a significant increase in left ventricular diastolic volume by both pindolol and propranolol on echocardiographic evaluation. Even though our patients were highly selected and all had well-documented coronary artery disease, angina pectoris, ischemic electrocardiographic response to treadmill testing, and no symptoms of congestive heart failure, their left ventricular volumes and pressures (estimated from previous cardiac catheterization) varied widely. It is possible that a beta blocker agent could produce a variable increase in left ventricular volume, thus increasing wall stress and

countering the reduction in myocardial oxygen demand through a reduced double-product. This could explain why some patients did not have an increase in exercise tolerance despite similar reductions in double-product. Alternatively, since coronary vasoreactivity to beta blockers may differ in individual patients,[10] a favorable reduction in myocardial oxygen consumption could be countered by decreased coronary supply to a variable degree. In addition to the potential to reduce total coronary flow by reducing beta-adrenergic vasodilatory influences, increases in wall tension and extravascular compressive force could cause a redistribution in coronary blood flow and produce relative subendocardial ischemia.

Placebo effect and other factors affecting angina: This study illustrates the importance of the placebo effect in the treatment of angina pectoris. Other studies[11,12] have found the incidence of angina pectoris to show a continued reduction for 8 to 11 weeks on placebo before leveling off. To negate this effect, drug studies in patients with angina pectoris should be placebo-controlled and done in a crossover design, and objective evaluation should be done with treadmill testing. Using this type of protocol, our study and that of Arstila et al.[4] did not show as much clinical improvement as other reported studies (Table II). However, repeat treadmill tests during this longer type study could produce a training effect. This could occur because of the extra exercise of the treadmill tests themselves, but it is more likely that the patients learn that they can safely exercise even to the point of angina and thus increase their daily activities. Our pedometer data suggest that this is a possibility, but we have no control data; that is, patients did not wear the pedometer before commencing the study. Finally, in a long-term study of angina pectoris, changes in underlying disease could occur through either progression or regression of atherosclerosis, changes in collateral circulation, or compensatory hypertrophy. However, significant changes should be unlikely in studies that are less than several months in duration.

Acknowledgment

We acknowledge with much appreciation the assistance of Drs. Richard Steckley and Eric Wooten in performing this study.

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Antiarrhythmic, Antifibrillatory, and Hemodynamic Actions of Bethanidine Sulfate: An Orally Effective Analog of Bretylium For Suppression of Ventricular Tachyarrhythmias

MARVIN B. BACANER, MD and DAVID G. BENDITT, MD

Bethanidine sulfate is a chemical and pharmacologic analog of bretylium tosylate that has virtually identical antifibrillatory and inotropic actions on the heart. Bretylium is the only drug approved by the Food and Drug Administration specifically for the "prophylaxis and treatment of ventricular fibrillation." Unlike bretylium, which is poorly absorbed from the gut and limited to parenteral use, oral bethanidine is absorbed rapidly. Bethanidine was given to 23 patients with recurrent multiple drug refractory ventricular tachycardia and fibrillation. Eighteen patients (78%) had complete suppression of spontaneous or electrophysiologically inducible tachyarrhythmias; 3 were improved and 2 had no benefit. In 6 of a 9 patient subgroup studied by programmed electrophysiologic drug testing, bethanidine completely prevented previously inducible ventricular tachyarrhythmias at the maximal stimulus tested (including 4 extrastimuli and burst-pacing at 10 times threshold). Cardiac output measured in 6 patients 1 to 2 hours after bethanidine was increased in 4, unchanged in 2, and decreased in 1. Ten patients on long-term therapy with bethanidine and protriptylene (to prevent orthostatic hypotension) have been free of arrhythmias from 2 to 26 (average 13) months.

Ventricular fibrillation (VF) is the major cause of death in our society.[1] Many cardiac patients at high risk of sudden death might be protected by prophylactic treatment with an orally effective drug that prevented VF.[2,3] At present, bretylium tosylate is the only drug approved by the Food and Drug Administration for the "prophylaxis and treatment of VF."[4] Bethanidine sulfate is a closely related chemical analog of bretylium tosylate which has virtually identical pharmacologic actions on the ventricle.[5–9] Unlike bretylium, which is poorly absorbed from the gut, oral bethanidine is absorbed rapidly.[5,10,11]

Bretylium tosylate suppresses and prevents VF and induces chemical ventricular defibrillation in experimental animals[6,12–23] and in man.[6,14,24–39] It is limited, however, to parenteral use because therapeutic levels are difficult to achieve and maintain by oral administration alone.[11,39] Because of disappointing therapeutic results in patients treated with oral bretylium to prevent out-of-hospital VF,[38,39] it was decided to reinvestigate the efficacy of bethanidine sulfate in the suppression of life-threatening ventricular arrhythmias in man.[5,40]

During our original studies in the early 1960s on the effect of sympatholytic drugs on VF, it was observed that bethanidine and bretylium had virtually identical antifibrillatory and inotropic actions on the canine ventricle.[5–8,41] More recent studies confirmed that bethanidine increased the VF threshold 150% in the normal canine heart and 327% in the infarcted heart and resulted in nonsustained VF.[7,8]

In pilot human trials bethanidine, like bretylium, also was effective in suppressing arrhythmias and VF.[5,40] Similarly, both drugs induced orthostatic hypotension.[9,11,24,28,40] In deciding in 1965 which drug to test in major clinical studies, bretylium was chosen because tolerance to orthostatic hypotension developed quickly, allowing patients to be ambulated.[24,28,31,39,42] In contrast, tolerance to orthostatic hypotension almost never developed during bethanidine treatment ([43] and unpublished observations). Thus, persistent orthostatic hypotension precluded the successful use of bethanidine as an antifibrillatory drug in ambulatory patients and studies were abandoned.

It has since been learned that orthostatic hypotension induced by both bretylium and bethanidine can be effectively antagonized by a variety of drugs, particularly tricyclic antidepressants such as protriptyline and desipramine which are believed to block the norepinephrine pump.[43,44] If bethanidine can be used in ambulatory patients by combined therapy with a tricyclic, this could be an effective oral means of preventing out-of-hospital VF.[40]

This report describes effects of bethanidine used together with protriptyline in 23 consecutive patients with current drug refractory ventricular tachycardia (VT) and VF.

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Methods

Patient selection: Twenty-three consecutive patients with repetitive unsustained VT (runs of 6 to 99 ventricular ectopic beats) or sustained VT (more than 100 beats) were treated with bethanidine because they could not be controlled by other antiarrhythmic drug regimes. Sixteen patients also had from 1 to 20 episodes of VF. The patients had a variety of heart diseases, and 16 patients had congestive heart failure when bethanidine was started.

All patients were accepted if (1) they had multiple episodes of out-of-hospital life-threatening VT and/or at least 1 episode of primary VF, (2) they could take oral medication, and (3) they gave informed consent. All other antiarrhythmic drugs were discontinued. In 10 patients, tachyarrhythmias were initially treated successfully with betylium before a trial of bethanidine. In each patient, bretylium was discontinued and treatment with bethanidine was not started until tachyarrhythmias reappeared to make certain that acute efficacy of bethanidine could be assessed clearly from the time course of the response.

Patients received a loading dose of bethanidine ranging from 3 to 30 mg/kg and a maintenance dose of 10 to 40 mg/kg per day. All patients also received protriptyline, 15 to 120 mg/day, in divided doses to antagonize orthostatic hypotension.

Specific drug testing by programmed electrophysiologic stimulation: Nine patients had cardiac catheterization to place electrodes for programmed electrophysiologic study. Each patient had had 1 or more cardiac arrests outside the hospital. In the initial electrophysiologic study, quadrapole catheter electrodes were positioned in the right atrium, His bundle, and right ventricle for recording, pacing, and stimulation. An arterial line was placed in 7 patients to assess the effect of bethanidine on cardiac output (measured by dye dilution).

The test routine was designed to induce VT by delivering from 1 to 4 programmed ventricular extrastimuli (at 2 times threshold current) to the right ventricle while it was paced at a cycle length range of 400 to 500 ms. A rest interval of at least 10 sinus beats was taken before introduction of extrastimuli. The program systematically added and shifted the extrastimuli in the cardiac cycle and varied the coupling interval. When VT could not be induced by 4 sequential extrastimuli, ventricular burst-pacing (6 to 10 beats) was used. Starting with a cycle length of 400 ms, it was progressively shortened to 230 ms or until 1-to-1 ventricular capture was no longer possible. The end point of the study was the induction of reproducible episodes of either unsustained or sustained VT or bursts of VF or flutter which were terminated by rapid right ventricular pacing or electrical cardioversion.

After VT was reproducibly induced during the control study, the test drug was administered and the procedure repeated. The test drugs used were bethanidine, quinidine, procainamide, and disopyramide. Starting with patient 5 (Table I), when bethanidine was found to prevent previously inducible tachyarrhythmia with 4 extrastimuli or burst-pacing at 2 times threshold (approximately 1 mA), the current strength was increased to 10 times threshold (8 mA, the maximal output of the current generator). The stimulus routine was then repeated as the ultimate test of bethanidine-induced resistance to initiation of ventricular tachyarrhythmia. The test dose of bethanidine ranged from 16 to 30 mg/kg. It was given with 10 to 15 mg of protriptyline to test the interaction with bethanidine. Cardiac output was measured in triplicate by indicator dilution technique before and again 1 to 2 hours after the oral loading dose of bethanidine.

TABLE I Programmed Electrophysiologic Drug Testing

	Extrastimuli to Induce VT/VF		Cardiac Output (liters/min)	
Case	Control	Bethanidine	Control	Bethanidine
1	2	NI	3.90	5.40
2	3	NI	4.50	5.15
3	3	NI	6.90	7.30
4	3	4	3.92	2.62
5	3	NI (10 t)	4.53	5.2
6	SVT	NI (10 t)	. . .	. . .
7	2	3	4.65	4.76
8	2	NI (10 t)	4.50	4.40
9	3	2	. . .	. . .

NI = not inducible at 2 times threshold; SVT = spontaneous ventricular tachycardia; 10 t = 10 times threshold.

Initially 16 mg/kg of bethanidine with 10 mg of protriptyline were given and tested 1 to 1.5 hours after administration. This was followed by a second 8 mg/kg dose tested 45 minutes later. The initial loading dose of bethanidine was increased to 20 mg/kg given with 15 mg of protriptyline. To exclude dose dependence, an additional dose of 10 mg/kg bethanidine was given if the initial dose did not completely prevent inducible arrhythmia with 4 extrastimuli or burst-pacing.

The order in which test drugs were given was varied randomly and 3 to 4 days were allowed for the previous drug to be eliminated. The doses of quinidine, procainamide, and disopyramide used were the highest doses considered safe as judged by changes in conduction and checked by measuring blood levels drawn immediately after the test procedure. Blood levels of bethanidine were measured in serial blood samples drawn during electrophysiologic drug studies.

Results

The patients included 16 men and 7 women aged 21 to 75 years (mean 53). Before treatment with bethanidine, all patients had recurrent episodes of ventricular tachyarrhythmias lasting 3 days to 1.5 years and 16 patients had episodes of VF. These tachyarrhythmias had not been suppressed by aggressive treatment with 3 or more antiarrhythmic drugs singly or in various combinations before bethanidine was administered. Bethanidine suppressed existing repetitive or electrically inducible VT and VF in 18 (78%) of 23 patients, none of whom had further tachyarrhythmia while on bethanidine. Ten patients in whom tachyarrhythmias had been previously suppressed with bretylium had recurrences 8 hours to 6 days after bretylium was discontinued. In each patient, bethanidine suppressed the recurring tachyarrhythmia as early as 6 minutes or as late as 5 hours after ingestion (Fig. 1 and 2). Delay greater than 2 hours in the onset of action and ultimate efficacy appeared dose-dependent in patients who received a starting dose less than 20 mg/kg. In 3 other patients with recurrent episodes of VT, tachyarrhythmias were temporarily suppressed or became more difficult to induce during programmed electrophysiologic drug testing. In 3 patients, bethanidine was effective but was discontinued because of side effects. In

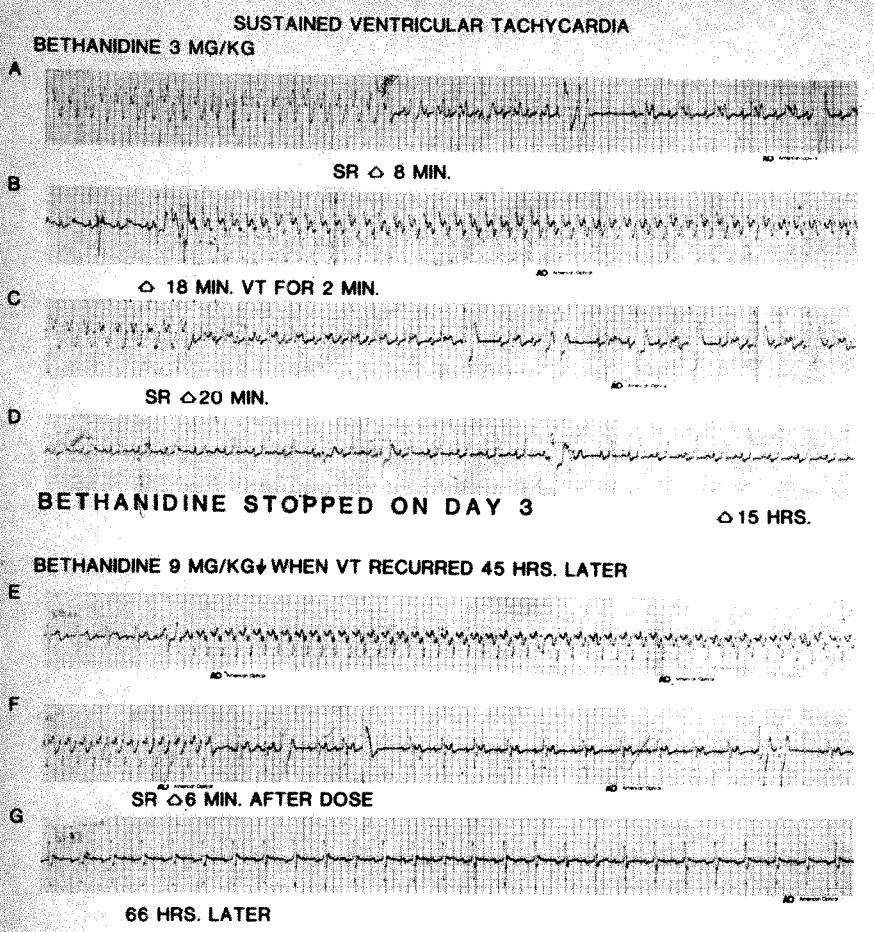


FIGURE 1. Record of 1 patient showing rapid conversion of sustained VT to sinus rhythm (SR) by oral bethanidine on 2 occasions (**strips A** and **C** and then again on **strip F**).

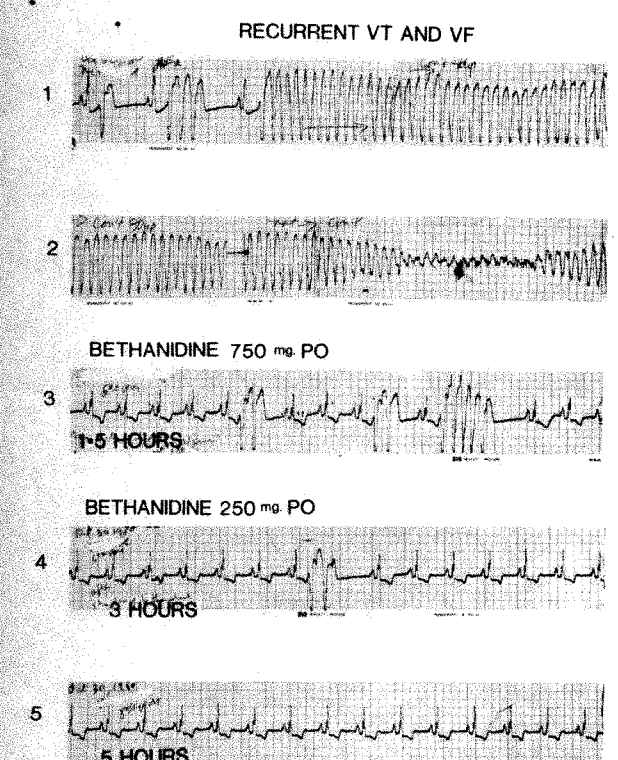


FIGURE 2. Record of a patient showing suppression of VT and VF by oral bethanidine. PO = by mouth.

2 patients bethanidine was of no value. Two patients died while receiving bethanidine.

Programmed electrophysiologic drug testing: In the control state 8 of the 9 patients had VT and/or VF-flutter inducible with 1, 2, or 3 programmed extrastimuli; the other patient was having frequent spontaneous episodes of unsustained VT during the control period and was too unstable for electrical induction to establish a control threshold.

Effect on stimulus tolerance: Bethanidine treatment (16 to 30 mg/kg) completely protected 6 of the 9 patients from inducible arrhythmia at the maximal stimulus intensity tested (Table I). Except for Patient 2 (Table I) who was protected by both bethanidine and quinidine, no other patient in this group received a drug other than bethanidine which prevented inducible arrhythmias at maximal stimulation. Three patients, who could not be induced by the usual provocation at 2 times threshold current after bethanidine, tolerated 4 extrastimuli and burst-pacing at a current 10 times above threshold (8 mA) without the induction of arrhythmias. Two other patients (Patients 4 and 8) were partly improved by bethanidine in that resistance to induction of VT increased from 3 to 4 extrastimuli, and from 2 to 3 extrastimuli. One patient had no benefit from any drug tested; all antiarrhythmic drugs appeared to make him worse.

Blood levels: After a 16 mg/kg dose, serial blood samples in 3 patients indicated that the bethanidine blood level rises rapidly to 0.18 to 0.25 μg/ml within 15 minutes. Bethanidine blood levels continued to rise to levels of 0.74 to 1.51 μm/ml 1.5 to 2 hours after ingestion where maximal protection against inducible arrhythmias was observed.

Effect of other antiarrhythmic drugs on stimulus tolerance: The effect of quinidine at doses up to 6 μg/ml blood levels was assessed in 4 patients, but only 1 patient had any benefit. In 2 patients VT became more easily inducible on quinidine than in the control state. Two patients who were well protected by bethanidine alone had no benefit from bethanidine when it was given immediately after quinidine testing.

Procainamide in doses up to 16.7 μg/ml and 10.4 μg/ml NAPA was studied in 5 patients, but none were protected at the maximal stimulus tested. One patient's tolerance increased from 3 to 4 extrastimuli before VT was induced. After administration of bethanidine, VT could not be induced in this patient with 4 extrastimuli or burst-pacing at 10 times threshold. Disopyramide was of no value in 2 patients tested. It was not tested in other patients because it was contraindicated by severe congestive heart failure.

Effect on cardiac hemodynamics: One to 2 hours after oral bethanidine, cardiac output and stroke volume increased in 4 patients, remained essentially unchanged in 2 patients, and decreased in 1 patient (Table I). Heart rate and supine blood pressure were essentially unchanged from control values.

Outpatient experience: Fifteen patients were discharged on doses of bethanidine ranging from 10 to 40 mg/kg per day and protriptyline 15 to 80 mg/day in divided doses, and 13 patients (86%) had no further episodes of VT or VF while on bethanidine. Although effective in suppressing ventricular tachyarrhythmia, bethanidine was discontinued in 3 patients: in 1 because of pregnancy, 1 because of anxiety over taking an investigational drug, and 1 because of persistent orthostatic hypotension. Two patients on bethanidine died after discharge from the hospital.

Long-term maintenance on bethanidine: Ten patients have been maintained on bethanidine from 2 to 26 months (average 13) with complete suppression of tachyarrhythmia. Periodic Holter monitor studies in all patients every 2 to 3 months have shown single ventricular ectopic beats and pairs but no triples or runs of VT, except as described later. When ectopic pairs were noted on the Holter record, the dose of bethanidine was increased by 50 to 100 mg/dose and adjusted to subsequent Holter findings. After 14 months on bethanidine 1 patient reported a brief episode of symptoms, which may have been a run of VT that disappeared 3 to 4 minutes after he took 700 mg of bethanidine. Except for that instance he has been free of symptoms for 26 months and has returned to full-time work for the past 22 months. One other patient had a single episode of VT 3 months after discharge, at which time the serum potassium level was 2.7 mEq/liter. Stable sinus rhythm was restored as soon as potassium was administered. Bethanidine treatment with potassium supplement was continued, and she has remained free of arrhythmia for the past 11.5 months.

Mortality: Four patients have died while on bethanidine, 2 while in the hospital. Despite satisfactory suppression of the arrhythmia, 1 died from a pulmonary embolus, and another from acute myocardial infarction with refractory intermittent VT not responsive to any drug including bethanidine. Both patients who died outside the hospital had severe congestive heart failure.

Discussion

Bethanidine was safe and effective in acutely suppressing both spontaneous and electrophysiologically inducible ventricular tachyarrhythmias in 78% of the 23 patients treated. Ten patients on long-term maintenance treatment with bethanidine and protriptyline have been free of tachyarrhythmia for 2 to 26 months (mean 13). All 23 patients had recurrent VT and 16 had 1 or more out-of-hospital cardiac arrests. These tachyarrhythmias had been previously refractory to at least 3 other antiarrhythmic drugs used singly or in various combinations. Sixteen patients had moderate to severe congestive heart failure.

Another potentially beneficial effect of bethanidine was its positive inotropic action,[8] which was manifested by an increase in cardiac output in two thirds of the patients tested. Because increased cardiac output was observed 1 to 2 hours after administration of bethanidine, it was unlikely to be solely an effect of catecholamine release, which would probably be much shorter in duration. The long-term effects on cardiac performance have not been assessed, but the patients maintained on bethanidine have shown no adverse hemodynamic effects.

Test of efficacy: The test of efficacy relied on each patient as his own control. Great care was taken to establish (1) that tachyarrhythmias were indeed repetitive and refractory to other drugs, and (2) that efficacy could be judged by an appropriate interval between the time bethanidine was administered and the time that sustained elimination of the arrhythmia occurred.

Electrophysiologic drug testing by programmed ventricular stimulation is widely accepted as a reproducible semiquantitative method of evaluating and matching the efficacy of a drug and its dose to a patient's specific arrhythmogenic cardiac disorder.[46-52] In our 9 patients undergoing programmed drug study, this was an acceptable controlled evaluation. In the other 14 patients the criteria for efficacy were less rigorous because evaluation of data was based on rhythm history and evidence of acute suppression. In each request for treatment with bethanidine, an experienced cardiologist indicated that either (1) the arrhythmias were persistent, lasting at least 3 days, (2) all other antiarrhythmic drugs tested had failed clinically, or (3) the arrhythmia was successfully suppressed with bretylium but an oral drug was also needed to send the patient home. In 10 patients in whom the arrhythmia was initially suppressed with bretylium, it was discon-

tinued and bethanidine was not administered until the tachyarrhythmia returned.

Dose-dependent efficacy: It also was apparent that the onset of action was dose-dependent (Fig. 1). With a low dose of bethanidine (3 mg/kg), initial conversion to sinus rhythm began in 8 minutes after ingestion and lasted 10 minutes, but was then interrupted on the 18th minute by another 2 minute burst of VT before definitive reversion to sinus rhythm occurred on the 20th minute after sufficient bethanidine had been absorbed. After 3 days bethanidine was stopped and 45 hours later VT returned. When a larger loading dose (9 mg/kg) was given for the second episode of VT, definitive conversion to sinus rhythm occurred after 6 minutes. Such a rapid response suggests that the therapeutic level of bethanidine needed to suppress VT had fallen to only slightly below the antiarrhythmic threshold concentration. Only 6 minutes were needed to absorb the small amount of bethanidine needed to bring the drug back to a therapeutic level.

The dose-dependent action of bethanidine was also demonstrable during programmed electrophysiologic drug testing when bethanidine was tested after administration of each additional dose and stimulus tolerance was observed to increase with each dose up to 30 mg/kg.

Electrophysiologic drug testing: The complete prevention of inducible arrhythmias in 6 of 9 patients and the partial protection in 2 others after bethanidine intake was a very favorable frequency of success for a single drug. Moreover, bethanidine was the only tested drug that was significantly effective in any patient except for quinidine in 1 patient. By comparison, reports on many antiarrhythmic drugs from centers using electrophysiotopic drug testing indicate that in only 30 to 50% of patients tested did any drug or combination of drugs prevent inducible tachyarrhythmia.[46–52]

The maximal number of extrastimuli used was progressively increased during the course of the study. When patients tolerated 3 extrastimuli and burst-pacing, 4 extrastimuli were tested. In later studies, when patients on bethanidine tolerated 4 extrastimuli and burst-pacing at 2 times threshold, the current was increased to the maximal current output of the system (8 mA), which was approximately 10 times threshold, and the test protocol was repeated. Of 3 patients subjected to this extreme provocation, none had inducible arrhythmia while on bethanidine, although arrhythmias were readily inducible in all in the control state or on other drugs. This was by far the most aggressive attempt to induce arrthythmias by programmed ventricular stimulation reported from any laboratory.[46–52]

It is true that the superthreshold stimulation was much greater than any provocation that can occur clinically short of electrocution. Nevertheless, bethanidine demonstrated a protective action that was not obtainable with any other antiarrhythmic drug tested. It remains to be established that such a test is clinically meaningful.

One potential value of superthreshold stimulation is that it may provide a basis for distinguishing between drugs when several drugs prevent inducible arrhythmias at stimulus levels usually employed.[46–52] In 1 patient, both quinidine and bethanidine prevented inducible arrhythmias with 4 extrastimuli or burst-pacing at twice threshold. This patient, therefore, was discharged on quinidine because it was prudent to use an approved drug rather than an investigational drug when both appeared equal in ability to prevent induced arrhythmias. The patient died suddenly 6 months after discharge. If an additional superthreshold challenge had shown that bethanidine was more protective than quinidine at 10 times threshold, the patient might have been discharged on bethanidine. Of the patients in whom bethanidine has been shown effective by electrophysiologic drug testing, none has died, whereas 2 patients discharged on other drugs died suddenly.

Drug antagonism: Bethanidine should not be given together with quinidine, which was found to antagonize its therapeutic effect in 2 patients. Similar antagonism to bretylium efficacy also has been reported with quinidine as well as procainamide and other cardiodepressant antiarrhythmic drugs.[6,24,31,53] Concomitant administration of bethanidine with other antiarrhythmic drugs or tricyclic antidepressants other than protriptyline probably should be avoided until compatibility can be demonstrated.

Pharmacologic side effects: The only significant side effect of bethanidine is orthostatic hypotension. No acute toxicity occurs in the dogs at 300 mg/kg, which is 10 times the highest therapeutic dose.[43] No chronic toxicity has been observed in monkeys or mice at 50 mg/kg per day.[43] Bethanidine induces postganglionic sympathetic blockade by blocking catecholamine release from sympathetic nerve endings, and the resulting chemical sympathectomy reduces peripheral resistance.[9] Blood pressure in the supine position may decrease but usually changes little because the positive inotropic effect usually increases cardiac output sufficiently to compensate for the decrease in peripheral resistance.[8] Orthostatic hypotension, however, is a regular pharmacologic side effect of bethanidine which is aggravated by inhibition of baroreceptor responses.[43]

Management of orthostatic hypotension: Concomitant administration of protriptyline was effective in antagonizing bethanidine-induced orthostatic hypotension in doses much lower than those used for antidepressant therapy. Protriptyline did not interfere with the antiarrhythmic-antifibrillatory actions of bethanidine as the arrhythmias remained suppressed after protriptyline was added. Indeed, some tricyclic antidepressants have been reported to increase the VF threshold.[54] Moreover, in our recent animal experiments, protriptyline alone increased the VF threshold and also had a synergistic interaction with bethanidine so that a combination of the 2 drugs increased the VF threshold higher than did either drug alone (unpublished observations).

The first 13 patients did not receive protriptyline until it was clear that their arrhythmias were suppressed by bethanidine. The dose of protriptyline needed to raise the VF threshold (5 mg/kg) was much higher than even the highest dose used to antagonize the orthostatic

hypotension, indicating that protriptyline itself does not account for the antiarrhythmic effect observed in patients on both drugs. Nortriptyline did not raise the VF threshold of the canine heart and appeared to antagonize bethanidine action (unpublished observations).

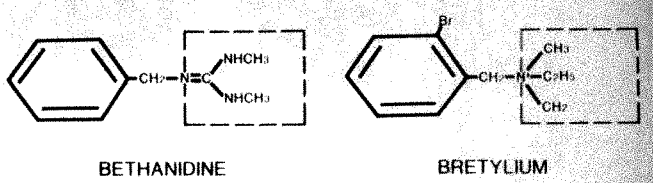
Despite effective suppression of arrhythmias, bethanidine was discontinued in 2 patients because of persistent orthostatic hypotension. One patient had severe congestive heart failure. He had an abnormally low resting cardiac output which was lowered still further by bethanidine; he was the only patient in which this occurred. Persistent orthostatic hypotension probably reflected a limited cardiac reserve, so that the decrease in peripheral resistance was not compensated by the positive inotropic action of bethanidine. In the second patient, bethanidine was discontinued because orthostatic hypotension persisted with 40 mg/day of protriptyline and at that time we were not yet using higher doses of protriptyline.

Bethanidine dosage: We started cautiously at the low end of the bethanidine dose (3 mg/kg) that was found to increase the VF threshold in the dog.[8] It became apparent in our first patient (Fig. 1) that this dose was marginal, so we quickly increased the loading dose. In the patients studied by electrophysiologic drug testing, it became apparent that 20 mg/kg followed by another 10 mg/kg, if needed, was generally effective in preventing inducible arrhythmia with bethanidine.

Guide to maintenance therapy: After the 20 mg/kg loading dose, maintenance therapy was started using 5 to 8 mg/kg bethanidine 4 times daily together with 30 to 80 mg/day of protriptyline in divided doses. Ambulation began with dangling the legs at the bedside and walking only with assistance. If symptoms of orthostasis persisted, the protriptyline dose was increased progressively until all symptoms (dizziness or syncope) were eliminated. One patient received 120 mg/day for 1 day, but this dose should not be continued for more than 1 day because of the possibility of an anticholinergic reaction. It is safer to take more time at doses of 60 to 80 mg/day. Patients were instructed to change to the upright position slowly to allow for slow adaptation to position changes and to take an extra 5 mg of protriptyline as necessary in addition to the regular doses if they became lightheaded after discharge. If protriptyline (15 mg TID) is given for 3 days before starting bethanidine the patients can be ambulated immediately (Robins AH, unpublished observations).

Bethanidine dosage was adjusted upward by 50 to 100 mg per dose or per alternate dose if pairs or triple ventricular extra beats were observed. No attempt was made to suppress single ventricular extra beats (even if frequent) or even short episodes of bigeminal rhythm. Long episodes may respond to an increase in dose, but the objective of treatment should be to prevent VT and VF by increasing the VF threshold so that premature beats are rendered harmless.

The antihypotensive action of protriptyline began about 4 hours after administration but took many hours or days to achieve maximal effect. Protriptyline tends to have cumulative effects, so after 4 to 6 weeks the protriptyline dose was reduced. This was done by reducing the dose by 5 mg/24 hours. After the initial adjustment period, most patients got along well on 15 to 30 mg/day of protriptyline. Impotence has occasionally been a bothersome side effect of sympathetic blockade but was eliminated by increasing the dose of protriptyline. One patient had persistent nausea which caused anorexia. Despite a good therapeutic response, bethanidine was discontinued and the nausea disappeared.



BETHANIDINE BRETYLIUM

FIGURE 3. Structural formula of bethanidine and bretylium. The **dashed lines** show the substitution of dimethylguanidine for quaternary ammonium removing the fixed positive charge that interferes with oral absorption of bretylium.

Comparison of bethanidine and bretylium: Bethanidine, like bretylium, is not in a free diffusion equilibrium with tissue but is selectively concentrated and bound in heart, sympathetic nerves, liver, and spleen.[55] The therapeutic effect of bretylium correlates with its myocardial and not its plasma concentration.[56] Bethanidine very likely has similar kinetic characteristics. Corder[57] has calculated the steady state volume distribution equilibrium for bethanidine at 2.7 liters/mg, which indicates that a large proportion of the drug is outside the bloodstream.

While similar in chemical structure and pharmacologic characteristics, bretylium is poorly absorbed from the gut because the strong fixed positive charge in the side chain limits lipid solubility.[39] In contrast, bethanidine is likely to be rapidly transported across the gut and into myocardial cells because the dimethylguanidine on the side chain is more lipid-soluble then the charged quanternary ammonium (Fig. 3). In dogs, the VF threshold rises 10 minutes after oral bethanidine.[8] The prompt suppression of VT also indicates a rapid onset of action in man (Fig. 1).

Adequate potassium required for efficacy: Bethanidine, like bretylium, probably acts directly on the myocardial cell, altering potassium, sodium, and calcium transport and distribution.[6,8] Specific studies on the mechanism of action of bethanidine, however, have not been done. An important element in bretylium efficacy, which also appears true for bethanidine, is that myocardial and serum potassium must be normal for the drug to be effective.[6,25] Neither drug appears to work well when potassium is depleted. Since many cardiac patients with arrhythmias are receiving diuretic agents, digitalis glycosides, and conventional antiarrhythmic drugs, all of which tend to deplete intracellular potassium, it is important to assess and restore myocardial potassium to normal levels in patients receiving bethanidine. Bethanidine tends to reduce serum potassium as potassium shifts into cells. Because serum potassium may be in the normal range even when

myocardial potassium is low, it is our practice to keep serum potassium in the high normal range (4.5 mEq/liter).

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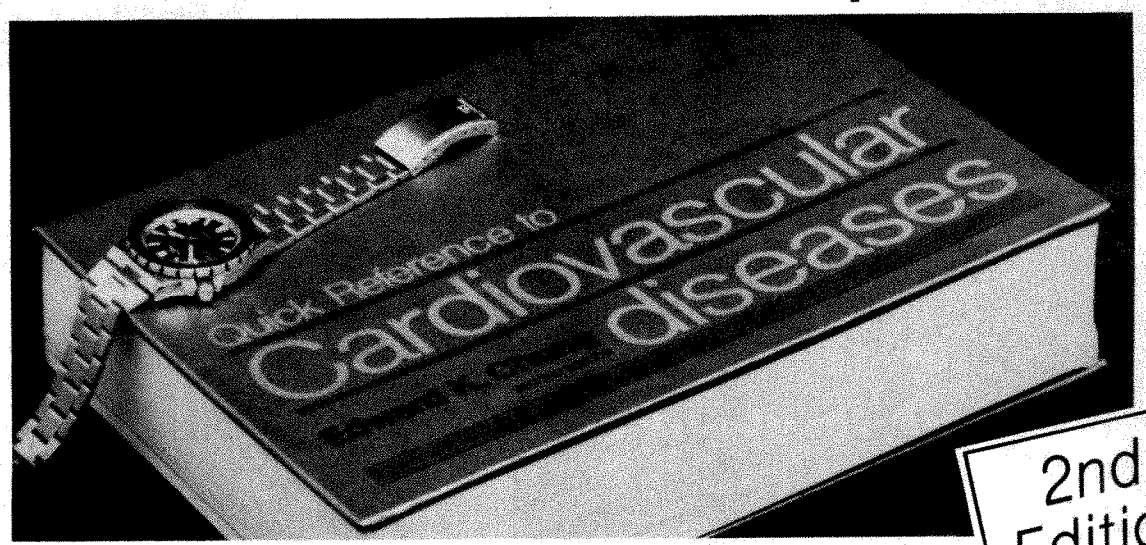

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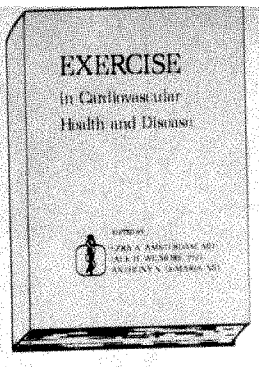

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EXERCISE in Cardiovascular Health and Disease

Edited by
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Jack H. Wilmore, PhD, Professor and Head Dept. of Physical Education & Athletics, Univ. Arizona
Anthony N. DeMaria, MD, Dir. Echocardiography Section, Univ. of Calif. School of Medicine

SEPTEMBER 1977, 408 PAGES, ILLUS

This comprehensive work covers every aspect of exercise and its role in Diagnosis, Treatment, and Prevention of cardiac disease.

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- Similar to an intravenous *infusion*, Transderm-Nitro delivers medication at a constant rate.
- Patients are protected against extremely high concentrations being reached even where skin is unusually permeable.

(actual size)

(approx. thinness)

Magnified cross section of Transderm-Nitro system

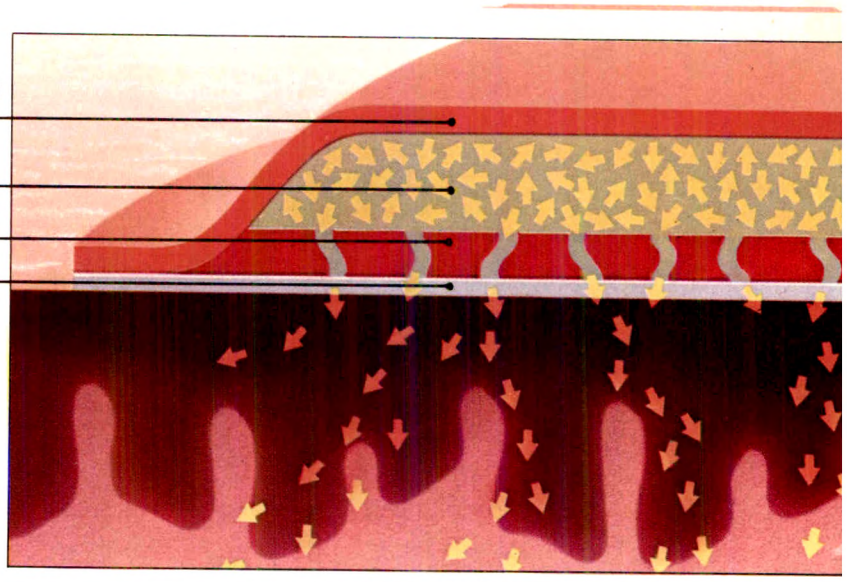
impermeable water-resistant backing layer

nitroglycerin reservoir

rate-controlling membrane

hypoallergenic contact adhesive

Contains an initial dose of medication to saturate skin-binding sites so that absorption begins immediately



Precision dosage system assures 24-hour angina protection

Steady, sustained 24-hour nitroglycerin levels

Constant protection against angina attacks assured by uninterrupted plasma concentrations of nitroglycerin: Transderm-Nitro 5 rated to release 5 mg/24 hours; Transderm-Nitro 10 rated to release 10 mg/24 hours.

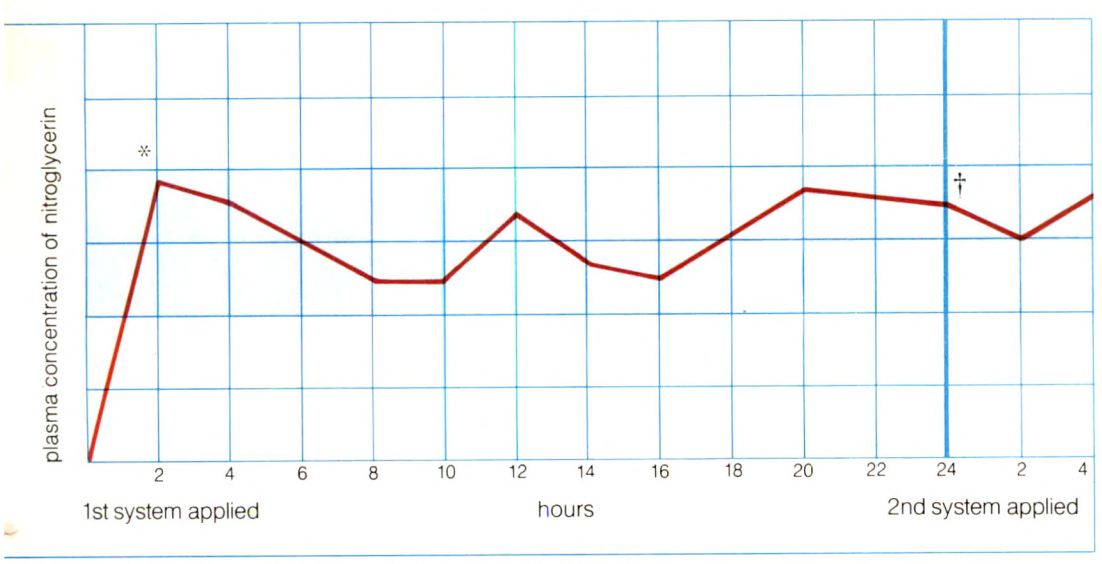
Orthostatic hypotension may indicate nitroglycerin overdosage; reduce dosage if symptoms occur. Nitrates are contraindicated in patients with increased intraocular pressure. Withdrawal should be gradual if treatment is terminated. Do not apply to distal parts of the arms and legs.

System is simple and easy to use

- Every 24 hours the old system is removed and the new one applied.
- Therapeutic effect can be anticipated 30 minutes after application and maintained for 30 minutes following removal.
- Can be applied anywhere on the body except the distal extremities.

An advance beyond tablets and ointments

- 24-hour sustained therapeutic blood levels of nitroglycerin
- Precise dosage control
- Ease of administration...avoids mess and inconvenience of ointments
- Once-a-day dosage to enhance compliance
- May be worn while swimming, bathing and showering



First measurement in this study was taken 2 hours. However, a therapeutic effect can be anticipated 30 minutes after application of the system, and will be maintained for 30 minutes after its removal.

†After 24 hours, system is removed and a new one is applied to another site. Renewal of the system does not result in any significant alteration in the plasma levels, as long as the change is made without delay.

CIBA

For full details, please see the prescribing information on the next page.

Transderm®-Nitro nitroglycerin

Once-a-day, 24-hour protection against angina attacks

System can be applied anywhere except distal extremities. Doesn't compromise daily activities.

Transderm®-Nitro
(nitroglycerin)
Transdermal Therapeutic System

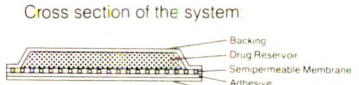
DESCRIPTION

Transderm-Nitro (nitroglycerin) transdermal therapeutic system is a flat unit designed to provide controlled release of nitroglycerin through a semipermeable membrane continuously for 24 hours following application to intact skin. Nitroglycerin (glyceryl trinitrate) is a prompt-acting vasodilator for the relief and prevention of anginal attacks. Systems are rated to release *in vivo* 5 and 10 mg nitroglycerin over 24 hours and are in sizes of 10 and 20 cm^2 respectively.

One-fifth of the total nitroglycerin in the system is delivered transdermally to the patient over 24 hours; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. The rated release of drug is dependent upon the area of the system. 0.5 mg nitroglycerin is delivered *in vivo* for every cm^2 of system size.

The Transderm-Nitro system comprises four layers as shown below. Proceeding from the visible surface toward the surface attached to the skin, these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid; 3) an ethylene/vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Cross section of the system:



ACTIONS

When the Transderm-Nitro system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In clinical studies transdermal absorption of nitroglycerin from a nitroglycerin system occurred in a continuous and well-controlled manner, for a minimum of 24 hours. Therapeutic effect can be anticipated 30 minutes after application of the system and to be maintained for 30 minutes after its removal.

INDICATIONS AND USAGE

Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS

Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS

In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS

Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS

Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION

Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response.

The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension, especially during orthostasis, indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.

Do not store above 86°F (30°C).

PATIENT INSTRUCTIONS FOR APPLICATIONS

A patient leaflet is supplied with the systems.

HOW SUPPLIED

Transderm-Nitro System Rated Release *in vivo*	Total Nitroglycerin in System	System Size	Carton Size
5 mg/24 hr	25 mg	10 cm^2	30 Systems (NDC 0083-2105-26)
5 mg/24 hr	25 mg	10 cm^2	7 Systems (NDC 0083-2105-07)
10 mg/24 hr	50 mg	20 cm^2	30 Systems (NDC 0083-2110-26)

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Continuous Monitoring of Left Ventricular Performance With The Computerized Nuclear Probe During Laryngoscopy and Intubation Before Coronary Artery Bypass Surgery

ROBERT W. GILES, MD, BS, HARVEY J. BERGER, MD, PAUL G. BARASH, MD, SANJIWAN TARABADKAR, MD, PETER G. MARX, BM, BCh, GRAEME L. HAMMOND, MD, ALEXANDER S. GEHA, MD, HILLEL LAKS, MD, and BARRY L. ZARET, MD

Left ventricular performance was monitored serially in 25 patients during laryngoscopy and intubation in the anesthetic induction period before elective coronary artery bypass surgery using the labeled equilibrium blood pool and the computerized nuclear probe. Left ventricular ejection fraction was obtained preoperatively, after induction of anesthesia but before endotracheal intubation, immediately after intubation, and at 1 minute intervals thereafter for 10 minutes. In all patients, there was an immediate decrease (mean 16%) in left ventricular ejection fraction accompanying the reflex hypertension and tachycardia occurring during laryngoscopy and endotracheal intubation; it was significantly depressed for 3 minutes with the concomitant hemodynamic changes. Seven patients did not demonstrate a recovery of left ventricular ejection fraction to the preintubation value. In 10 healthy noncardiac patients undergoing orthopedic surgery, after an identical anesthetic induction sequence and intubation, there was a similar decrease in ejection fraction, but of shorter duration. In these patients the recovery of left ventricular performance preceded the recovery of blood pressure and heart rate.

This study demonstrates that profound decreases in left ventricular performance accompany the reflex hypertension and tachycardia occurring during endotracheal intubation and that there is persisting depression of left ventricular function in some patients with coronary artery disease. These findings indicate the potential utility of the computerized nuclear probe for monitoring ventricular performance during this critical period.

Reflex vasoconstriction may result in substantial pathophysiologic consequences in patients with coronary artery disease. During induction of anesthesia, laryngoscopy and intubation can be associated with reflex hypertension and tachycardia due to autonomic stimulation.[1,2] In patients with coronary artery disease, these hemodynamic alterations may lead to an imbalance in myocardial oxygen supply-demand relationships at the time of anesthesia.[3] This may result in myocardial ischemia, impairment in cardiac performance, and if sustained, myocardial necrosis. In addition, acute alterations in afterload may affect ventricular function directly.

In the present study, we monitored left ventricular performance during laryngoscopy and endotracheal intubation in patients undergoing elective coronary artery bypass surgery. Global left ventricular performance was monitored using the computerized nuclear probe, a radiation detector system that provides accurate continuous sampling of data necessary for assessment of rapidly changing reflex events.[4-6] Radionuclide variables were obtained simultaneously with hemodynamic and electrocardiographic data.

From the Cardiology Section, Department of Internal Medicine; Nuclear Medicine Section, Department of Diagnostic Radiology; Department of Anesthesiology; and the Cardiothoracic Surgical Section, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut. Supported in part by a grant-in-aid from the American Heart Association (81-1080). Dr. Giles was an Overseas Clinical Fellow of the National Heart Foundation of Australia. Dr. Berger is an Established Investigator of the American Heart Association. Manuscript received February 17, 1982; revised manuscript received April 19, 1982, accepted April 26, 1982.

Address for reprints: Barry L. Zaret, MD, Cardiology Section, Yale University School of Medicine, 333 Cedar Street, 87 LMP, New Haven, Connecticut 06510.

Methods

Patient population: We studied 25 patients (24 men, 1 woman) with symptomatic coronary artery disease undergoing elective coronary artery bypass surgery. Their mean age was 57 years (range 38 to 68). Thirteen patients had had a previous myocardial infarction 1 month to 19 years before the present study. All patients had stable angina pectoris. Six were in New York Heart Association functional class I or II, and 19 were in class III or IV. Patients with unstable or preinfarction angina or associated valvular heart disease and those undergoing left ventricular aneurysm resection were excluded. Decisions on patient participation were based on the patient's and referring physician's consent as well as laboratory logistics. The population studied was a representative but nonconsecutive sample of those undergoing elective coronary revascularization surgery at Yale-New Haven Hospital. Twenty-three patients were receiving propranolol at a mean dose of 240 mg/day (range 60 to 680). Propranolol was continued until 4 hours before surgery. Nineteen patients were receiving long-acting nitrates, 4 were receiving digoxin, and 6 were receiving diuretics.

Preoperatively, the mean left ventricular ejection fraction in the group was 57% (range 26 to 82) determined by gated equilibrium cardiac blood pool imaging (see later). Fifteen of the 25 patients had a normal ejection fraction (greater than 55%). Twenty patients had triple vessel disease (including 1 patient with left main coronary artery stenosis), 4 patients had double vessel disease, and 1 patient had a single lesion involving the left anterior descending artery. This study was approved by the Yale University School of Medicine Human Investigation Committee, and informed consent was obtained from all patients.

Preoperative and operative protocol: On the day before surgery, left ventricular performance was measured both with the computerized nuclear probe (Bios) and conventional scintillation camera gated blood pool imaging. Camera studies were performed with a single crystal scintillation camera (Siemens LEM) interfaced to a nuclear medicine computer system (Medical Data Systems Mugacart). Left ventricular ejection fraction determined by the nuclear probe and multigated blood pool imaging correlated closely ($r = 0.92$). This finding is comparable to previously reported correlations from this and other laboratories.[5-9]

On the day of surgery, after premedication and placing of intravascular monitoring catheters, the patient's blood pool was labelled and the nuclear probe was positioned. Hemodynamic and radionuclide data were obtained before induction immediately before laryngoscopy (baseline), during laryngoscopy and intubation, and at 1 minute intervals thereafter for 10 minutes. The preintubation values serve as baseline data for the study since they represent the final hemodynamic steady state before the intervention of laryngoscopy and endotracheal intubation. Particular care was taken to ensure the stability of the probe's position on the chest during laryngoscopy and intubation.

Nuclear probe technique: The patient's red blood cells were labelled in vivo with 20 to 25 mCi of technetium-99m pertechnetate. The probe was positioned at the left ventricular and background regions of interest, using positioning algorithms and operator routines developed and validated in this laboratory.[6] Left ventricular ejection fraction is calculated from background-corrected end-diastolic and end-systolic counts. These calculations assume a stable equilibrium blood pool and constant background level. The background activity level is recorded at the beginning of the induction of anesthesia and is automatically decay corrected during the study period (approximately 20 minutes). The variability of manually derived beat-to-beat ejection fraction is ±5.8% (in absolute ejection fraction units). This represents twice the pooled standard deviation of ejection fraction measurements in 710 individual beats analyzed in 71 patients.[6] Based upon these variability data, a value of 6% or greater was used in the present study to signify a nonrandom change.

Changes in end-diastolic counts and the difference between end-diastolic and end-systolic counts also indicate proportional changes in end-diastolic volume and stroke volume, respectively. The microprocessor of the nuclear probe calculates and displays the mean beat-to-beat ejection fraction, relative change in end-diastolic counts and stroke counts, and relative change in derived cardiac output on a 10 second sweep. These data were used for analysis. The analog data from the nuclear probe also were interfaced to a multichannel strip chart recorder allowing simultaneous recording of the electrocardiogram, pressure measurements, and radionuclide time-activity curves (Fig. 1).

Anesthetic technique: A standard anesthesia sequence for patients undergoing electric coronary artery bypass surgery at this institution was used. All patients received a similar pharmacologic induction sequence and were monitored in a comparable manner. Premedication with morphine sulphate (0.15 mg/kg) and scopolamine (0.4 mg) was administered intramuscularly 90 minutes before arrival in the operating room. All patients were adequately sedated on arrival at the operating room and no patient exhibited evidence of myocardial ischemia. At the time of arrival in the operating room, a thermodilution quadruple lumen catheter was positioned in the pulmonary artery percutaneously by way of the internal jugular vein. A radial artery catheter also was placed for recording systemic blood pressure. All measurements were obtained at end-exhalation. A standard electrocardiographic V_5 lead was monitored continuously throughout the study period. Arterial oxygen and carbon dioxide tensions and pH were assessed before intubation, at intubation, and 10 minutes after intubation.

Anesthesia was induced with intravenous diazepam (0.3 mg/kg) and nitrous oxide/oxygen (3:2). Enflurane inhalation was titrated as clinically indicated for adequate depth of anesthesia. During induction and before laryngoscopy and intubation, the patients were hemodynamically stable with maintenance of cardiac output. Muscle relaxation for laryngoscopy and endotracheal intubation was achieved with a continuous infusion of succinylcholine (0.2% solution). Laryngoscopy and endotracheal intubation were performed with a #3 MacIntosh blade laryngoscope and an 8.0 mm tube lubricated with a nonanesthetic water-soluble gel. The duration of laryngoscopy and intubation averaged 11 seconds (range 4 to 22). All patients received enflurane after intubation, and 10 patients received enflurane before laryngoscopy and intubation. In terms of clinical, angiographic, and functional assessment as well as hemodynamic responses during the study, these 10 patients were indistinguishable from those who did not receive enflurane before intubation. Thus, the data from all 25 patients are analyzed together.

Technique controls: To assess possible changes in background activity (a factor that could influence ejection fraction measurements) induced by laryngoscopy and intubation, 2 patients undergoing coronary artery bypass surgery were studied with the probe positioned over the background region of interest for the entire induction period. The same study protocol was used; however, only background activity was counted. An assumption is made that background activity remains relatively stable throughout the study period. Unrecognized changes in background activity during anesthesia

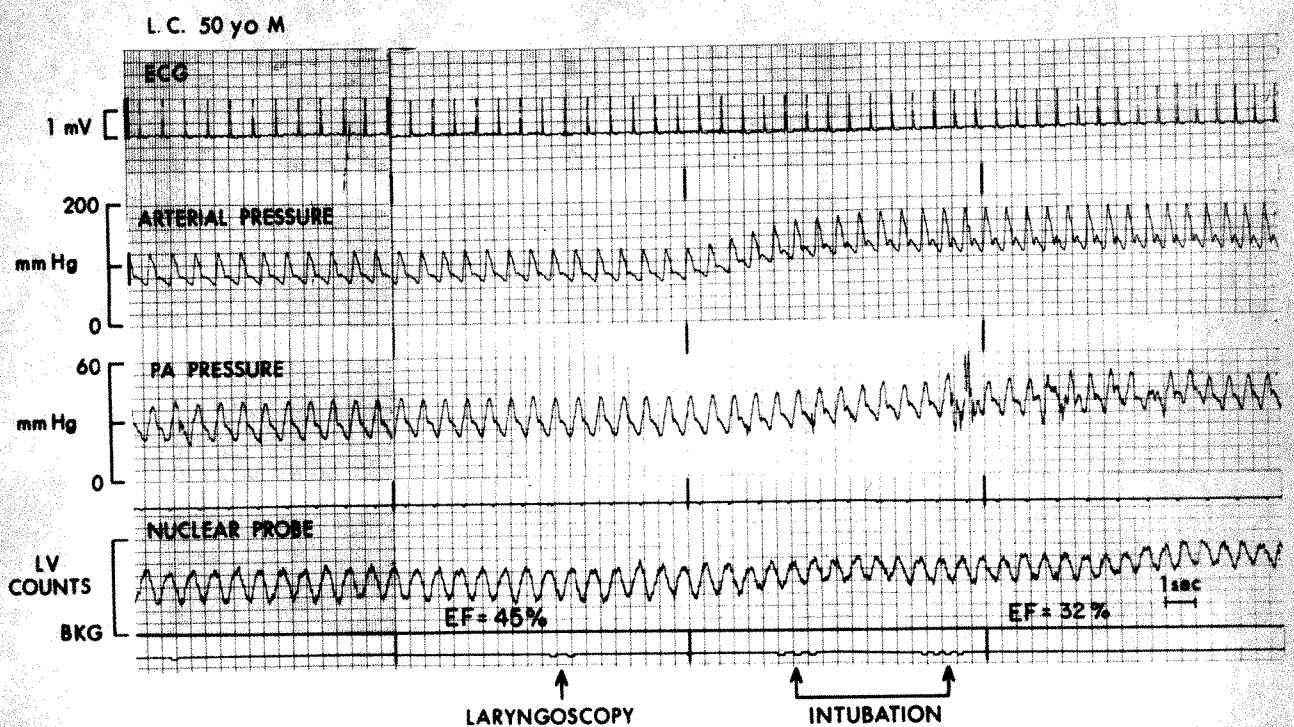

FIGURE 1. Simultaneous recording of the electrocardiogram (ECG), arterial pressure, pulmonary artery (PA) pressure, and radionuclide left ventricular (LV) time-activity curve (NUCLEAR PROBE). **Arrows** indicate the beginning of laryngoscopy and the actual time for intubation. Arterial pressure increases within 5 seconds of the beginning of laryngoscopy accompanied by increases in heart rate and PA pressure. Left ventricular ejection fraction (EF) is 45% before intubation, and decreases to 32% within 15 seconds after laryngoscopy and intubation. BKG = background activity level.

induction would affect the reliability of serial determinations of ejection fraction because the background level is recorded at the beginning of the study and used for all subsequent calculations. In these 2 patients the relative change in background counts was less than ±2% of the preintubation value. The change in background counts was calculated to result in a maximum of ±4% absolute change in ejection fraction (ejection fraction [EF] units) due to potential changes in background activity during the study period.

To assess possible changes in ejection fraction due to assisted ventilation, this was performed in 3 cooperative conscious patients on the day before surgery using a face mask in a manner comparable to that employed during induction of anesthesia. Probe monitoring of ejection fraction was obtained during this period. In these patients, airway pressures similar to those recorded during induction were achieved to simulate the changes in intrathoracic pressure during assisted ventilation after muscle relaxants are administered. There was less than a ±3% absolute change in the recorded ejection fraction in these patients.

Healthy noncardiac patients (control group): Ten healthy patients aged 20 to 32 years (mean 25) without clinical or electrocardiographic evidence of cardiac disease, undergoing elective orthopedic surgical procedures also were studied. Premedication, anesthesia induction, laryngoscopy, and intubation were performed exactly as in the patients with coronary artery disease. In this group, invasive intravascular monitoring was not performed. Blood pressures were measured externally by a Dynamap (model 845) which noninvasively determines blood pressure at 30 second intervals. The nuclear probe protocol was identical to that in the study group.

Statistical analysis: Analysis of variance for repeated measures was performed using the general linear model of the Statistical Analysis System.[10] Contrasts were obtained between preintubation baseline data and subsequent serial determinations. Group data are presented as the least squares mean ± least squares standard error. The changes in hemodynamic and functional variables at intubation in various patient groups were compared by Student's *t* test. Changes in ejection fraction are expressed in ejection fraction units. The time to recovery of ejection fraction is expressed as the median value and compared in the 2 study groups by the Wilcoxon rank sum test.[11] Probability (p) less than 0.05 was considered significant.

Results

Patients with coronary artery disease (Table I): Hemodynamic and ventricular performance variables were stable until the period of laryngoscopy and intubation. However, all patients with coronary disease had an immediate decrease in left ventricular ejection fraction associated with laryngoscopy and intubation (Fig. 2). Absolute decrease in ejection fraction ranged from 4 to 26% (EF units). Ejection fraction decreased from 50 ± 3% at preintubation to 34 ± 3% at intubation ($p < 0.0001$), and remained significantly decreased for 3 minutes after intubation (45 ± 3%, $p < 0.002$). Systolic blood pressure increased from 116 ± 4 before intubation to 152 ± 3 mm Hg at intubation ($p < 0.0001$) and remained significantly elevated for 3 minutes after intubation ($p < 0.045$). Heart rate increased from 57 ± 3 to

TABLE I Effects of Intubation on Left Ventricular Function in Patients With Coronary Artery Disease (n = 25)

Period	LVEF (%)	p	Systolic BP (mm Hg)	p	HR (bpm)	p	PCWP (mm Hg)	p	EDC (%)	p
Preintubation	50 ± 3	...	116 ± 3	...	57 ± 3	...	16 ± 2	...	100%	...
Intubation	34 ± 3	<0.0001	152 ± 3	<0.0001	72 ± 3	<0.0001	23 ± 2	<0.0001	97 ± 2	NS
1 minute	38 ± 3	<0.0001	153 ± 5	<0.0001	78 ± 3	<0.0001	19 ± 2	<0.009	98 ± 2	NS
2 minutes	44 ± 3	<0.0001	131 ± 5	<0.0001	71 ± 3	<0.0001	22 ± 2	<0.008	99 ± 2	NS
3 minutes	45 ± 5	<0.002	122 ± 4	<0.045	66 ± 3	<0.0001	19 ± 2	NS	102 ± 2	NS
4 minutes	50 ± 3	NS	117 ± 5	NS	61 ± 3	NS	19 ± 2	NS	103 ± 2	NS
5 minutes	47 ± 3	NS	114 ± 4	NS	59 ± 3	NS	16 ± 2	NS	102 ± 2	NS
10 minutes	47 ± 3	NS	109 ± 4	NS	55 ± 3	NS	19 ± 2	NS	102 ± 2	NS

Results are expressed at least squares mean ± least squares standard error. Data are compared with preintubation values. Overall each variable except EDC had highly significant effects ($p < 0.0001$). BP = blood pressure; EDC = end-diastolic counts as a percentage of the preintubation value; HR = heart rate in beats/min (bpm); LVEF = left ventricular ejection fraction; NS = not significant (<0.05); PCWP = pulmonary capillary wedge pressure.

71 ± 3 beats/min at intubation ($p < 0.0001$). Heart rate was elevated significantly for 3 minutes after intubation. Although pulmonary capillary wedge pressure increased from 16 ± 3 to 23 ± 2 mm Hg at intubation ($p < 0.0001$), the duration was less prolonged than for either heart rate or blood pressure changes; significant elevation was noted for 2 minutes after intubation (Fig. 2). End-diastolic counts did not change throughout the study (p = NS). At intubation, stroke counts decreased by 31 ± 4% ($p < 0.0001$); the time course paralleled that for ejection fraction. Neither cardiac index, determined by the thermodilution technique, nor relative cardiac output, determined by the probe, changed significantly. Cardiac index was comparable at preintubation and intubation (2.7 ± 0.14 versus 2.9 ± 0.15 liters/min per m^2, p = NS). As would be anticipated from the changes in blood pressure and cardiac index, peripheral vascular resistance increased by 22% during intubation.

The median time to recovery of left ventricular ejection fraction after intubation was 4 minutes (range 2 to 10). In 7 of the 25 patients, ejection fraction did not return to less than 6% (intrinsic variability) of preintubation values by 10 minutes after intubation (Fig. 3). In comparison with the baseline value, the final ejection fraction was 6 to 21% lower. These 7 patients were not distinguishable preoperatively or by baseline clinical or hemodynamic measurements from the 18 patients with full recovery of ejection fraction. In these 7 patients, comparing preintubation to intubation, the systolic blood pressure increased by 42 ± 12 mm Hg, while the heart rate increased by 13 ± 5 beats/min. These changes were not significantly different from the response seen in the 18 patients who had a full recovery

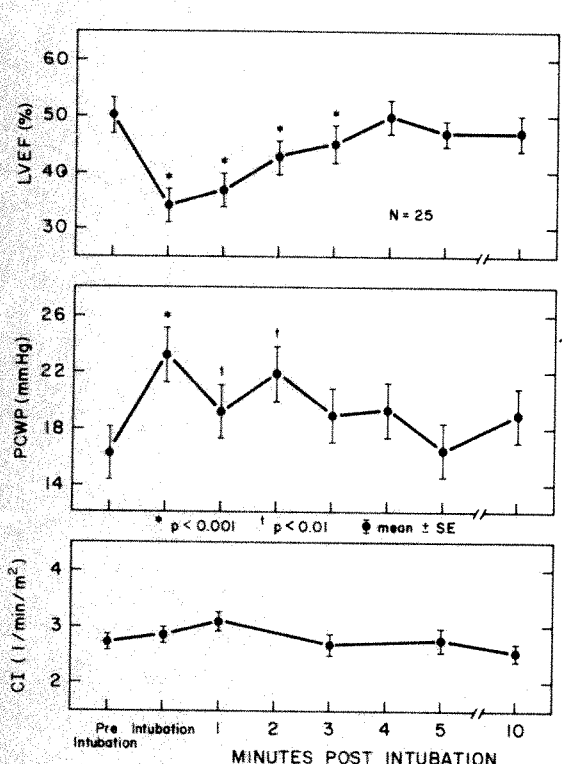

FIGURE 2. Group data for left ventricular ejection fraction (LVEF), pulmonary capillary wedge pressure (PCWP), and thermodilution cardiac index (CI) in patients with coronary artery disease. Results are expressed as least squares mean ± least squares standard error. Data are compared with preintubation values using analysis of variance for repeated measures. Note that LVEF remained depressed for 3 minutes after intubation while PCWP was elevated through 2 minutes. (The cardiac index was not obtained in all patients at 2 and 4 minutes and therefore is not shown.)

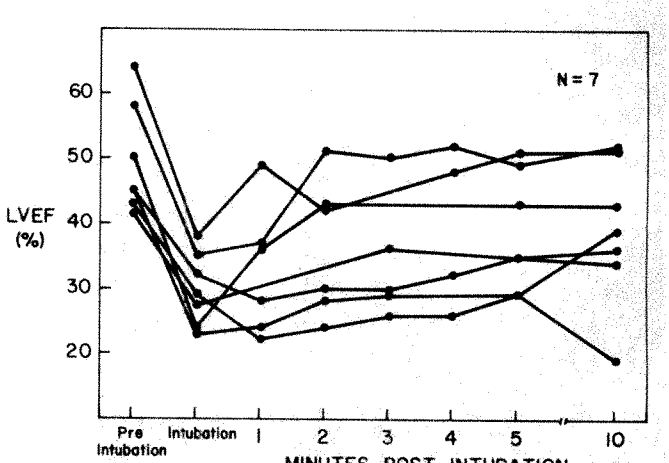

FIGURE 3. Individual left ventricular ejection fraction (LVEF) measurements at specific times during the study period in 7 patients who showed persisting depression of ejection fraction 10 minutes after laryngoscopy and intubation. In none of these patients did the value return to preintubation levels.

TABLE II Effects of Intubation on Left Ventricular Function in Healthy Noncardiac Patients (Control Subjects)

Period	LVEF (%)	p	Systolic BP (mm Hg)	p	HR (bpm)	p	EDC (%)	p
Preintubation	67 ± 3	. . .	107 ± 3	. . .	68 ± 5	. . .	100	. . .
Intubation	48 ± 3	<0.0001	116 ± 3	<0.013	77 ± 5	<0.011	101 ± 2	NS
1 minute	61 ± 3	<0.009	123 ± 3	<0.0001	88 ± 5	<0.0001	100 ± 2	NS
2 minutes	67 ± 2	NS	123 ± 3	<0.0001	87 ± 5	<0.0001	98 ± 2	NS
3 minutes	66 ± 2	NS	116 ± 3	<0.006	80 ± 5	<0.0007	100 ± 2	NS
4 minutes	66 ± 3	NS	108 ± 3	<0.025	71 ± 5	<0.001	98 ± 2	NS
5 minutes	68 ± 3	NS	111 ± 3	NS	75 ± 5	NS	97 ± 2	NS
10 minutes	69 ± 3	NS	106 ± 4	NS	66 ± 6	NS	98 ± 3	NS

Results are expressed as least squares mean ± least squares standard error. Data are compared with preintubation values. Overall each variable except EDC had highly significant effects ($p < 0.0001$). Abbreviations as in Table I.

of ejection fraction after intubation (35 ± 5 mm Hg and 16 ± 3 beats/min, respectively). Although the left ventricular ejection fraction remained depressed after intubation, systolic blood pressure was elevated only through 1 minute after induction ($p < 0.0005$), and heart rate only through 3 minutes ($p < 0.035$). Pulmonary capillary wedge pressure remained significantly elevated for 3 minutes after intubation (18 ± 2 mm Hg before intubation versus 25 ± 3 mm Hg 3 minutes after intubation, $p < 0.02$) in these 7 patients, whereas it was elevated only for the immediate postintubation period in the 18 patients who had a recovery of ejection fraction (18 ± 2 mm Hg before intubation versus 20 ± 2 mm Hg at intubation, $p < 0.002$). Only 2 patients showed ischemic electrocardiographic changes (1.0 mm or greater flat or downsloping S-T segment depression compared with the baseline value); neither was receiving digoxin. Both patients were among the 7 patients who showed persistent depression of ejection fraction 10 minutes after intubation.

Healthy noncardiac patients (Table II): The 10 healthy noncardiac patients, who were receiving no cardiac medication, showed transient decreases in ejection fraction ranging from 3 to 34% (mean 19 ± 3) with intubation. The ejection fraction was 67 ± 3% before intubation and decreased to 48 ± 3% at intubation ($p < 0.0001$). The ejection fraction remained significantly different from preintubation values 1 minute after intubation ($p < 0.009$). The median time to recovery after intubation was 2 minutes (range 1 to 4). This was significantly less than in the patients with coronary artery disease ($p < 0.01$). Moreover, the recovery of ejection fraction preceded the recovery of heart rate and blood pressure, which remained significantly elevated for 4 minutes after intubation ($p < 0.025$). Stroke counts decreased 28 ± 3% at intubation compared with the preintubation value ($p < 0.0002$) and paralleled the changes in ejection fraction. No significant changes in end-diastolic counts or relative cardiac output were noted during the study period.

Discussion

Ventricular function during operative laryngoscopy and intubation: This study demonstrates that the reflex hypertension and tachycardia associated with laryngoscopy and intubation result in profound decreases in left ventricular ejection fraction in patients with coronary artery disease undergoing revascularization surgery. Changes in ventricular performance generally occurred in the absence of ischemic electrocardiographic abnormalities, highlighting the potential value of this radionuclide probe technique for monitoring cardiac patients during this period. In 7 of 25 patients, depressed left ventricular ejection fraction compared with preintubation values persisted for the 10 minute monitoring period after intubation. The delayed recovery of ventricular function may indicate ongoing myocardial ischemia or damage, or both or altered ventricular reserve following afterload stress in the absence of ischemia. However, this period represents only 1 portion of the operative procedure during which myocardial damage could occur.[12] Further stress, such as hypertension during sternotomy[3] or inadequate myocardial protection[12,13] also could account for ischemia and infarction. The early operative period of anesthesia induction, laryngoscopy, and intubation should be viewed as a time for the potential initiation of a series of pathophysiologic events that may lead to hemodynamic compromise.

Although the patients with coronary disease studied in this report were clinically stable and were undergoing elective coronary revascularization, all were symptomatic and had extensive disease. Therefore, extrapolating these results to all patients with coronary artery disease undergoing both cardiac and noncardiac surgery should be done cautiously. Nevertheless, despite continued improvement in cardiac surgical techniques and improved methods of myocardial preservation, a distinct incidence of perioperative infarction after coronary surgery still persists.[12,14,15] Several studies also have demonstrated a substantial risk of postoperative infarction in cardiac patients undergoing noncardiac surgery.[16,17]

Mechanisms: Several potential mechanisms may explain our observations. The depression of left ventricular performance is probably a manifestation of altered functional reserve in the face of an acute increase in afterload[18] ("afterload mismatch"). The average increase in blood pressure in these patients was 36 mm Hg. Although left ventricular filling pressure is increased, failure to increase left ventricular end-diastolic volume suggests that the left ventricle in coronary dis-

ease may not be capable of evoking adequate preload reserve.[19] Alternatively, a limited ability to augment coronary flow in response to an acute increase in myocardial oxygen demands may result in myocardial ischemia and functional depression.

Another possible mechanism involves alterations in coronary vascular resistance or coronary artery spasm associated with laryngoscopy and intubation. The magnitude of decrease in ejection fraction, which is substantially greater than noted routinely during exercise-induced ischemia in coronary artery disease,[20] suggests that supply as well as demand may be altered. Mechanistically, this could parallel cold pressor stimulation,[21] an event resulting in altered coronary resistance and peripheral vascular resistance changes comparable to those observed during laryngoscopy and intubation. Alterations in coronary vascular resistance after cold pressor stimulation appear to be mediated by alpha-adrenergic mechanisms.[21] Most patients in our study were receiving substantial doses of propranolol at the time of surgery. Such beta-adrenergic blockade may result in unopposed accentuated alpha-adrenergic effects in both the peripheral and coronary circulations.[22] Propranolol also may limit the ventricular response to acute afterload stress in these patients.

Comparison with observations in normal persons: Major decreases in left ventricular ejection fraction also were observed in healthy noncardiac patients undergoing a comparable anesthetic protocol. We recognize that these patients were not age-matched to the coronary study group, nor were they intended to represent a control population. It virtually would be impossible to obtain an appropriate age-matched group undergoing elective surgery in whom angiography had recently ruled out significant coronary artery disease. The ejection fraction in this group fell by a degree comparable to that seen in the coronary patients; however, the decrease in ejection fraction was sustained for a shorter period of time after intubation than in the coronary patients. This temporal difference between groups could be dependent upon coronary disease, as well as patient age or propranolol therapy. Even the normal ventricle will manifest depression in performance when faced with a marked acute increase in afterload.[18,23] However, sympathetic stimulation may result in enhanced myocardial performance.[19] In these healthy noncardiac patients, the recovery of left ventricular performance preceded the recovery of altered afterload.

Methodology: The computerized nuclear probe appears to be an appropriate instrument for monitoring ventricular performance in the operating room. The ability to obtain serial data concerning global ventricular function on a beat-to-beat basis[5,6,24,25,26] provides a means of studying rapidly changing pathophysiologic reflex events such as those observed in this investigation. Such analysis would not be possible using conventional scintillation camera techniques. Studies involving technique controls indicate clearly that the results obtained are not a function of artifacts induced by either probe positioning or changes in background activity.

Implications of study: In patients with clinically significant heart disease, hypertension and tachycardia have been noted frequently with a wide variety of anesthetic induction techniques.[27–29] Although deeper levels of anesthesia associated with high concentrations of potent inhalation agents may blunt this response, the circulatory depression observed in patients with compromised cardiovascular function render this an unsatisfactory approach.[30] However, it is relevant to note that the hypertensive and tachycardic responses have been blunted, but not consistently eliminated, by topical oral pharyngeal anesthesia,[31] and the hypertensive effects have been eliminated through the use of vasodilators such as nitroprusside.[32] Preliminary studies have shown that the left ventricular responses to laryngoscopy and intubation may be blocked by the use of the high potency synthetic narcotic, fentanyl, as an anesthetic agent.[33] Thus, a variety of therapeutic options may be available for limiting or altering this ventricular response. However, further long-term studies are needed to assess the overall value of radionuclide monitoring in this period and its relation to subsequent patient outcome.

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Constrictive Pericarditis as a Complication of Cardiac Surgery: Recognition of an Entity

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Among 5,207 adult patients who underwent cardiac surgery, postoperative constrictive pericarditis was recognized in 11 patients (0.2% incidence rate). Seven patients had coronary arterial bypass grafting and 4 had valve replacement; the pericardium was left open in all cases. The average interval between surgery and presentation of pericardial constriction was 82 days (range 14 to 186). M mode echocardiography revealed epicardial and pericardial thickening in 7 cases and variable degrees of posterior pericardial effusion in 5 cases. Cardiac catheterization demonstrated uniformity of diastolic pressures with a characteristic early diastolic dip and late plateau pattern. Two patients responded to medical therapy for chronic pericarditis. One patient had a limited parietal pericardiectomy followed by recurrent constrictive pericarditis that eventually stabilized with medical therapy. The other 8 patients required radical pericardiectomy.

The pathophysiology of constriction after surgery is unclear. Its clinical expression involves a wide spectrum of presentation and therapeutic response. Constrictive pericarditis may be a complication of cardiac surgery in spite of an open pericardium and should be considered in postoperative patients who present with deteriorating cardiac function.

The cause of pericardial constriction is varied and ranges from idiopathic to the major categories of hereditary factors, infection, connective tissue disorders, metabolic disorders, trauma, radiation, and neoplasm.[1] Although open heart surgery involves a degree of trauma to the pericardium, constrictive pericarditis has been considered a rare complication of cardiac surgery,[2] especially when the pericardium is left open. However, several case reports[3-9] of constrictive pericarditis after such surgery have appeared.

In our institution, a small cluster of patients presenting with pericardial constriction after cardiac surgery was recently recognized.[10] This prompted us to review our overall experience with this condition. In this paper we summarize the clinical presentation of constrictive pericarditis as a complication of cardiac surgery in order to set guidelines for the recognition and management of this entity.

Methods

Study patients: Among 5,207 patients undergoing cardiac surgery at Emory University Hospital from 1969 through 1979, postoperative constrictive pericarditis was recognized in 11 patients. The hospital charts, diagnostic studies, cardiac catheterization data, operative reports, pathologic specimens, and follow-up data on these patients were retrospectively reviewed.

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The patients (Table I) consisted of 10 men and 1 woman, aged 32 to 64 years (mean 53). All patients had cardiac catheterization for the diagnosis of their primary cardiac disease. Seven patients underwent coronary arterial bypass graft surgery for severe coronary atherosclerotic heart disease. Three patients with rheumatic heart disease required mitral valve replacement. One patient underwent aortic valve replacement for calcific aortic stenosis.

The surgical technique included the following common procedures: (1) median sternotomy, (2) cardiopulmonary bypass with systemic hypothermia at 28°C, (3) cardioplegic arrest, (4) local topical hypothermia with iced saline solution, (5) pericardial irrigation, and (6) pericardium left open on sternal closure.

Diagnostic studies: Long-term evaluation was performed by primary care cardiologists in the community with periodic referral to the Emory University Clinic. Criteria for the diagnosis of constrictive pericarditis after cardiac surgery were: (1) symptoms and signs; (2) diagnostic studies such as electrocardiogram, chest X-ray film, and M mode echocardiogram suggesting constrictive pericarditis; (3) cardiac catheterization hemodynamic data compatible with a constrictive physiology; and (4) confirmation of constrictive pathology at the time of reoperation with improved hemodynamics after pericardial stripping—or resolution of the clinical manifestations of pericardial constriction after medical therapy directed toward chronic pericarditis.

Results

Initial Cardiac Surgery

Pericardial irrigant solutions (Table I): Of particular note are 5 cases (Cases 4 to 8) that occurred during the time that a povidone-iodine solution was utilized as a myocardial-pericardial irrigant on the basis of reports that it improved antisepsis of the open me-

TABLE I Patient Profile

Patient	Age (yr) & Sex	Initial Surgery	Surgical Date	Pericardial Irrigant at Time of Original Surgery	Definitive Presentation of Constrictive Pericarditis (days)	Therapy
1	49M	CABG-2	3/76	Antibiotic*	87	S
2	63M	CABG-4 MVR	3/77	Antibiotic*	160	S
3	57F	CABG-1	6/78	Isotonic saline	186	S+M
4	65M	CABG-2	11/78	Povidone-iodine†	45	S
5	44M	CABG-4	11/78	Povidone-iodine†	110	S
6	54M	AVR	12/78	Povidone-iodine†	66	S
7	64M	CABG-3	12/73	Povidone-iodine†	67	S
8	60M	CABG-3	1/79	Povidone-iodine†	81	S
9	44M	MVR	3/79	Isotonic saline	14	M
10	47M	CABG-2	4/79	Isotonic saline	61	M
11	32M	MVR	5/79	Isotonic saline	29	S

AVR = aortic valve replacement; CABG = coronary arterial bypass surgery and number of vessels bypassed; M = medical therapy (diuretic drugs, anti-inflammatory agents or steroids, or both); MVR = mitral valve replacement; S = surgical therapy (radical pericardiectomy).
* 80 mg gentamicin sulfate, 1 g cephalothin and 1,000 cc normal saline solution. † Concentrations varying from 1:20 to 1:1 povidone-iodine (Betadine®) and normal saline solution.

diastinum.[11,12] An antibiotic solution was used in 2 patients (Cases 1 and 2), and 4 patients (Cases 3, 9, 10 and 11) had irrigation with isotonic saline solution. In the retrospective review, there was no consistent record to determine the frequency with which each of the 3 irrigation solutions was used in the 5,207 patients undergoing cardiac surgery. The type of pericardial irrigation solution utilized was determined by the individual surgeon's preference.

Postoperative events (Table II): Temporary epicardial atrial and ventricular pacemaker wires were placed in 5 patients before chest closure. All of these wires were removed 3 to 5 days after surgery without apparent excessive bleeding or cardiac tamponade. Mediastinal chest tube drainage was normal except in 1 patient (Case 8) who required postoperative exploration for excessive hemorrhage.

During the postoperative period, only 1 patient (Case 7) had diffuse S-T and T wave electrocardiographic changes compatible with acute pericarditis. Chest X-ray films demonstrated pericardial air in 1 patient and a moderate increase in the cardiac silhouette in 3 patients. Transient postoperative hypertension requiring therapy with intravenous nitroprusside was observed in 6 patients but was not associated with excessive mediastinal bleeding. Some type of early postoperative pericardial event was seen in 7 patients; 2 patients had a pericardial rub that required no therapy, whereas 5 patients had symptoms and signs of pericarditis that necessitated therapy with either steroids or indomethacin or both.

No significant coagulation abnormalities were documented before cardiac surgery, during heparin reversal after cardiopulmonary bypass or in the postoperative period. No patients were given anticoagulant therapy, aspirin, procainamide, hydralazine or diphenylhydantoin. The 4 patients who underwent valve replacement all received a porcine heterograft and did not require long-term anticoagulant therapy.

TABLE II Initial Cardiac Surgery: Postoperative Events

Case	Temporary Pacemaker	Mediastinal Drainage Through Chest Tubes (3 day total [ml])	ECG	Chest X-ray Film	Arrhythmia	Hypertension	Pericarditis
1	No	498	NS	NS	No	Transient	No
2	No	425	NS	PA	Atrial fib	Chronic	P
3	Epicardial	595	NS	NS	No	No	No
4	No	670	NS	NS	No	Transient	Rub only
5	Epicardial	690	NS	NS	No	Transient	No
6	Epicardial	706	NS	NS	No	Transient	Rub only
7	No	2325	PC	ICS	No	Chronic	I
8	No	440	NS	NS	No	Transient	I + P
9	Epicardial	1570* Day 1	NS	NS	Atrial fib	No	No
10	No	1050	NS	ICS	No	Transient	I
11	Epicardial	1140	NS	ICS	Atrial fib	No	I + P

* Patient required reoperation for sternal bleeding, postoperatively on day 1.
ECG = electrocardiogram; fib = fibrillation; I = indomethacin; ICS = increased cardiac silhouette; NS = change not significant; P = prednisone therapy; PA = pericardial air; PC = changes consistent with pericarditis.

TABLE III Presentation of Constrictive Pericarditis

Case	Symptoms	Signs	ECG	Chest X-ray Film	Echo
1	Pericarditic pain, dyspnea	Elevated JVD, prominent *x* & *y*, pericardial knock	Nonspec. ST-T	ICS	PSM, EPT
2	Dyspnea, peripheral edema	Elevated JVD, pericardial knock	NS	NS	. . .
3	Peripheral edema, dyspnea	Elevated JVD	NS	NS	PVWNL, ASM
4	Dyspnea	Elevated JVD, prominent *x* & *y*, pericardial rub	LV	ICS	PSM, EPT, PPE
5	Pericarditic pain, dyspnea	Elevated JVD, prominent *x* & *y*	Nonspec. ST-T	NS	EPT, PPE
6	Dyspnea	Elevated JVD, prominent *x* & *y*, pericardial rub	NS	NS	PSM, EPT, PPE
7	Dyspnea	Elevated JVD	Nonspec. ST-T LV	ICS	ASM, EPT
8	Pericarditic pain, dyspnea	Elevated JVD, prominent *x* & *y*	Nonspec. ST-T LV	ICS	EPT, PPE
9	Dyspnea, peripheral edema	Elevated JVD, prominent *x* & *y*, pericardial knock	NS	ICS	PSM, PPE, PVWNL
10	Pericarditic pain, dyspnea	Elevated JVD, prominent *x* & *y*, pericardial rub	Nonspec. ST-T	ICS	. . .
11	Dyspnea, peripheral edema	Elevated JVD, prominent *x* & *y*	Nonspec. ST-T	NS	PSM, PVWNL

ASM = abnormal septal motion; ECG = electrocardiogram; Echo = echocardiogram; EPT = epicardial and pericardial thickening; ICS = increased cardiac silhouette; JVD = jugular venous distention; LV = low voltage; Nonspec. ST-T = nonspecific ST-T wave changes; NS = changes not significant; PPE = posterior pericardial effusion; PSM = paradoxical septal motion; PVWNL = prosthetic valve within normal limits; *x* = *x* descent; *y* = *y* descent.

Presentation of Constrictive Pericarditis

Clinical presentation (Table III): Definitive presentation of the symptoms and signs of constrictive pericarditis occurred an average of 82 days after cardiac surgery (range 14 to 186 days) (Table I). All patients had dyspnea and 4 complained of pericarditic chest pain. On physical examination, all patients had some degree of jugular venous distension, and a prominent *x* or *y* descent, or both, was evident in 8 patients. In no case was a significant paradoxical pulse elicited. A pericardial knock was heard in 3 patients and a rub was detected in 3 others. Six patients had pedal edema; 4 had evidence of ascites.

Evaluation of electrocardiographic changes revealed diffuse nonspecific ST-T wave changes in 6 patients and decreased QRS voltage in 3. A moderate increase in the cardiac silhouette on chest X-ray film was seen in 6 patients.

M mode echocardiogram (Table III): Seven patients had evidence of abnormal septal motion. Epicardial and pericardial thickening was seen in 7 patients. In 5 cases, variable degrees of posterior pericardial effusion were present (Fig. 1) but no anterior effusion was detected. Four of these patients with effusion (Cases 4, 5, 6, and 8) eventually underwent pericardiectomy and were found to have a significant posterior pericardial hematoma.

Cardiac catheterization (Table IV): An elevated diastolic plateau between the pressures in the right atrium, right ventricle, pulmonary artery, pulmonary capillary wedge position, and left ventricle (Fig. 2) was present in all but 1 case. Patient 3 had a discrepancy between a right atrial mean pressure of 12 mm Hg and a pulmonary capillary wedge mean pressure of 24 mm Hg, but did demonstrate an equal diastolic plateau between the right ventricle, pulmonary artery, pulmonary wedge, and left ventricle in addition to right atrial and right ventricular waveforms characteristic of constriction. A previous limited parietal pericardiectomy and evidence of generalized left ventricular hypokinesia in this patient may account for the discrepancy.

The right atrial tracing in all cases revealed a characteristic M or W pattern with prominent *x* and *y* descents (Fig. 3). Six patients (Cases 3, 5 to 8 and 11) had moderate prominence of the *y* descent. Of these 6, 3 patients (Cases 5, 6, and 8) had a posterior pericardial effusion on M mode echocardiography with a loculated pericardial hematoma found at the time of repeat surgery. In addition, Patient 4 had equalization of *x* and *y* descents with similar echocardiographic and pathologic findings. The equalization of *x* and *y* waves in this patient and the lack of a significantly dominant *y* wave in the other 6 patients are more consistent with the seroeffusive or elastic pattern of pericarditis described by Hancock[13,14] than with a rigid constriction in which the *y* wave is markedly dominant. Ironically, the 2 patients (Cases 9 and 10) who had a markedly dominant *y* descent suggestive of rigid shell constriction both responded to therapy with diuretic drugs and steroids and did not require pericardiectomy.

The right ventricular tracing in all cases demonstrated an early diastolic dip and a late diastolic plateau (square root sign) that equalized with the left ventricular end-diastolic pressure. In most cases, the right ventricular early diastolic dip did not approach absolute zero and was not always accompanied by a concomitant left ventricular early diastolic dip (Fig. 3) as one would expect in chronic rigid constriction. This divergence from the classic constriction pattern may be attribut-

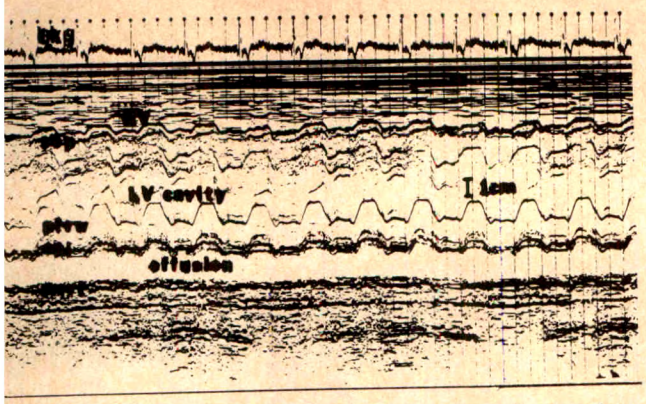

FIGURE 1. Patient 6. Representative M mode echocardiogram, demonstrating boxlike paradoxical interventricular septal (sep) motion and rapid anterior systolic motion of the posterior left ventricular wall (plvw) and epicardium (epi) with flattening in mid and late diastole—all consistent with constrictive pericarditis. In addition, epicardial and pericardial (peri) thickening is present with a significant posterior pericardial effusion. On reoperation, this patient was found to have an organized posterior pericardial hematoma with extensive pericardial fibrosis and constriction. ekg = electrocardiogram; LV = left ventricular; RV = right ventricle.

able to the presence of a more elastic form of constriction.

All the patients had definite constrictive hemodynamics in the resting state. It was not necessary to employ the rapid volume expansion technique of Bush et al.[15] No pericardiocentesis was attempted in view of the lack of evidence for a large anterior effusion.

In a few cases, biplane left ventricular angiography revealed a degree of "square wave" paradoxical septal motion. But overall, there was no consistent sign on either left ventricular or coronary angiography to distinguish pericardial constriction. In the patients with coronary arterial bypass surgery, repeat coronary angiography showed no major progression of disease in native vessels. All saphenous vein grafts were patent except in Patient 5, who had 1 blocked graft. In the patients who had had valve replacement surgery, prosthetic valve function was normal with no significant gradient or regurgitation documented.

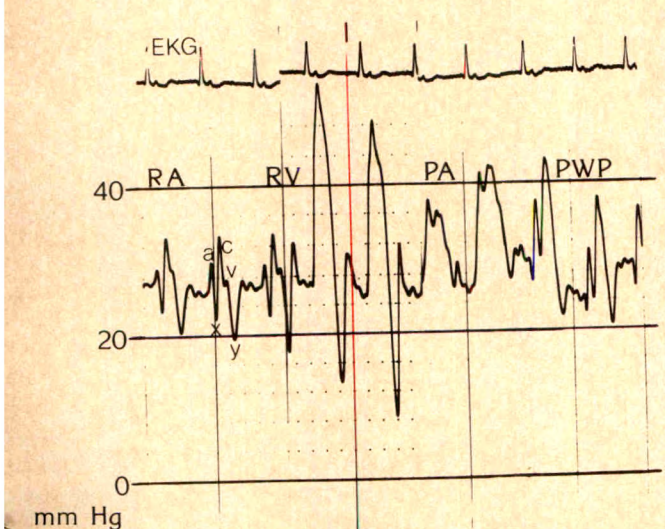

FIGURE 2. Patient 6. Continuous hemodynamic pressure tracings demonstrating a characteristic late diastolic plateau indicative of constriction between the right atrium (RA), right ventricle (RV), pulmonary capillary wedge pressure (PWP), and left ventricular end-diastolic pressure. The right atrial and right ventricular contours are consistent with constriction. Other abbreviations as in Figure 1.

Treatment of Constrictive Pericarditis

After the diagnosis of constrictive pericarditis was made, all patients at some time had a trial of medical therapy of 2 to 8 weeks' duration for chronic pericarditis. Therapy consisted of administration of diuretic drugs (variable doses of furosemide) and steroids (prednisone, 20 to 40 mg/day) or indomethacin (25 mg, 4 times daily). Only 3 patients (Cases 3, 9, and 10) showed improvement and did not require surgery. The remaining 8 patients eventually required radical pericardiectomy.

Medical therapy: The 3 patients who responded to medical therapy form an atypical group that deserves special attention.

Patient 3 was a 55 year old woman who had mitral valve replacement for severe rheumatic mitral regurgitation. She presented approximately 6 months later with constrictive pericarditis and underwent a limited parietal pericardiectomy. Two months after that procedure, cardiac catheterization again demonstrated the hemodynamics of persistent constriction with significant global left ventricular hypokinesia. Institution of a medical regimen of digoxin, diuretic drugs, and steroids for treatment of chronic pericarditis resulted in res-

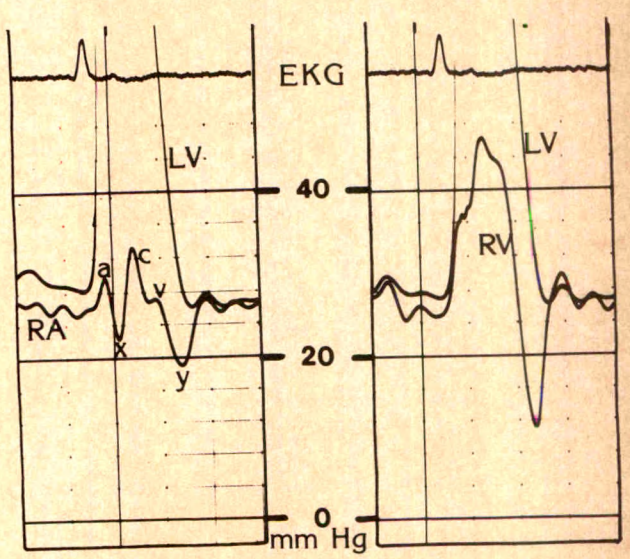

FIGURE 3. Patient 6. Simultaneous right and left heart hemodynamic pressure tracings demonstrating a right atrial (RA) pattern with moderately prominent *y* descent and a right ventricular (RV) early diastolic dip and late plateau. Late diastolic equalization of the pressures in the right atrium, right ventricle, and left ventricle (LV) is present. The right ventricular diastolic dip has not approached zero. The left ventricle does not have an early diastolic dip to correspond to the right atrial *y* wave or the right ventricular early diastolic dip. These patterns may suggest an elastic or seroeffusive form of constriction rather than a rigid constriction. Parenthetically, this patient was found to have a loculated posterior pericardial hematoma and effusion in addition to a fibrotic pericardium at the time of reoperation.

TABLE IV Cardiac Catheterization Data

Case	RA (mm Hg)	Pressures (mm Hg) RV	PA	Mean PWP	LV	Ao	CI (liters/2 min/m²)	LV gram	SVG
1*	*a* = 16, *v* = 18, m = 14	26/16	26/16	16	130/16	130/76	2.1	U	P
2*	m = 17	34/18	33/18 (24)	17	80/18	80/48	2.3	U	P
3	*a* = 14, *v* = 16, m = 12, *x* = 2, *y* = 4	42/20	42/24 (32)	24	126/22	122/72	2.5	H	P
4	m = 19, *x* = 7, *y* = 7	46/22	46/24	24	125/24	122/70	. . .	U	P
5	*a* = 26, *v* = 26, m = 25, *x* = 1, *y* = 6	50/26	48/27 (34)	30	170/29	138/88	3.1	U	B-1
6	*v* = 34, *x* = 3, *y* = 6, m = 27	50/27	40/28 (33)	30	136/28	138/82	1.3	U	. . .
7	m = 18, *x* = 7, *y* = 9	36/18	37/22 (26)	21	150/23	152/82	1.3	U	P
8	*a* = 25, *v* = 22, *x* = 6, *y* = 8, m = 20	40/22	40/21 (36)	21	140/25	138/85	1.6	U	P
9	*c* = 36, *v* = 34, m = 30, *x* = 2, *y* = 23	72/32	68/34 (42)	32	148/30	140/92	. . .	U	. . .
10	*a* = 18, *v* = 20, *x* = 8, *y* = 16	50/24	48/22 (28)	22	160/22	160/80	. . .	U	P
11	*c* = 26, *v* = 24, m = 22, *x* = 4, *y* = 8	46/22	42/24 (34)	28	114/24	118/76	2.2	U	. . .

* Original pressure tracings for Patients 1 and 2 were not available to document degree of *x* and *y* descents.
a = *a* wave; Ao = aorta; B = blocked graft plus number; *c* = *c* wave; CI = cardiac index; H = hypokinesia; LV = left ventricle; LV gram = left ventriculogram; m = mean pressure; P = patient; PA = pulmonary arterial; PWP = pulmonary wedge pressure; RA = right atrium; RV = right ventricle; SVG = saphenous vein graft; U = unchanged; *v* = *v* wave; *x* = *x* descent; *y* = *y* descent.

olution of constrictive signs. This case probably represents a constriction of the remaining visceral pericardium with a coexisting congestive cardiomyopathy.

Patient 9 was a 44 year old man who had signs of constrictive pericarditis 14 days after mitral valve replacement. A large posterior pericardial effusion was seen on M mode echocardiography. Repeat cardiac catheterization revealed hemodynamics of constriction. He responded dramatically to medical therapy consisting of administration of diuretic drugs and steroids. In view of the early presentation, this case may represent a late cardiac tamponade or seroeffusive constriction without the development of true fibrosis.

Patient 10 was a 47 year old man whose course after coronary arterial bypass surgery was complicated by recurrent pericarditis and findings of pericardial constriction confirmed by catheterization 2 months later. The clinical signs resolved with a regimen of diuretic drugs and steroids. This case may represent a less advanced form of pericardial fibrosis with a reversible seroeffusive component.

To date, none of the 3 patients have had a recurrence of their pericardial constriction signs or have required pericardiectomy. Steroid and diuretic therapy was successfully discontinued within an average of 2 months.

Surgical therapy: All 8 patients who underwent radical pericardiectomy were found to have extensive parietal and visceral hemorrhagic pericardial fibrosis. An organized hematoma was identified in 4 patients (Cases 4 to 6 and 8) (Fig. 4). Microscopic examination of excised pericardium revealed acute and chronic inflammation with areas of hemorrhage and fibrinous deposition. Bacterial, acid-fast bacillus, and fungal cultures were negative.

Intraoperative hemodynamic monitoring confirmed reversal of constrictive physiology on removal of the parietal and visceral pericardium (Fig. 5). All of the patients demonstrated hemodynamic and clinical improvement after pericardial stripping. The extensive radical pericardiectomy resulted in a nicked saphenous

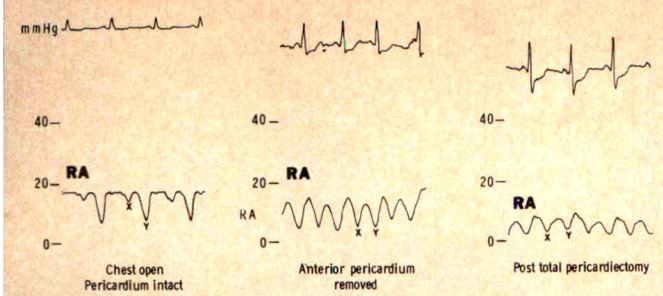

FIGURE 4. Patient 1. Intraoperative hemodynamic monitoring demonstrates (1) elevated right atrial (RA) pressures and dominant *y* descent with pericardium intact; (2) reduced right atrial pressures and equalization of *x* and *y* descents with anterior parietal pericardial stripping; (3) normalization of right atrial pressure tracing after parietal and visceral pericardiectomy.

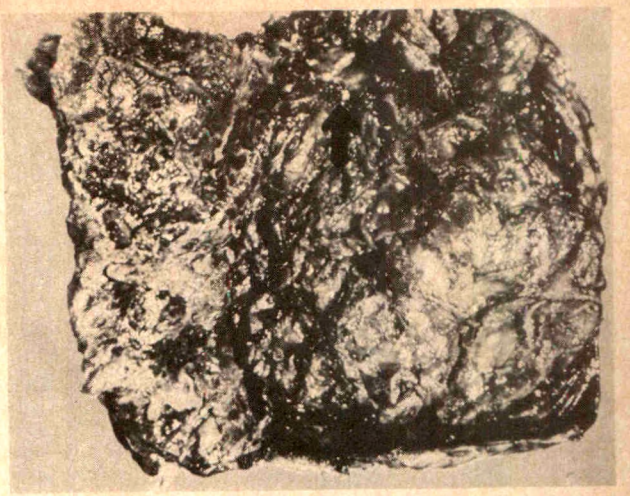

FIGURE 5. Patient 8. Surgical specimen; posterior pericardium. There is evidence of extensive gross hemorrhagic and fibrinous changes. A well organized loculated hematoma is present at the **top part** of the specimen.

vein graft in 2 patients and postoperative exploration for mediastinal bleeding in 2 patients. There was no mortality. To date, all of the surgically treated patients have continued to do well.

Discussion

Pathophysiology: In constrictive pericarditis both the parietal and visceral pericardium are involved in an inflammatory or infiltrative process resulting in fibrosis and eventual impediment to cardiac filling. Trauma to the pericardium in the course of cardiac surgery would seem to offer the appropriate setting for this sequence of events. Hemopericardium secondary to traumatic injury has been reported to lead to pericardial constriction.[16] There has been evidence that air-drying or chemical exposure[17] may destroy the normal fibrinolytic activity of pericardial serosal tissue resulting in a potential nidus for thrombus, adhesions and reactive fibrosis.[18]

Both immediate[19] and late[20] postoperative cardiac tamponade have been reported to be occasional complications of cardiac surgery. The site of postoperative bleeding is extrapericardial in most cases.[21] An open pericardium may actually serve as a collecting reservoir for blood. Our finding of an organized hematoma in the posterior pericardial space in 4 of 8 patients who required pericardiectomy points to the likelihood of old loculated hemorrhage as a pivotal event in the process of inflammation, fibrosis, and constriction.

Additional trauma may be inflicted on the pericardium by the use of pericardial irrigants. Cold injury to the myocardium and pericardium, including fibroplastic proliferation of pericardial serosal surfaces, has been reported[22] when a continuous iced saline slush solution at 0.5°C was used for local hypothermia. In clinical practice, iced saline solutions at temperatures of 2 to 4°C are utilized and rarely decrease the myocardial temperature below 10°C. Recent studies have not detected significant epicardial injury during prolonged topical hypothermia of 5°C to the myocardium.[23] Although local hypothermic solutions under normal conditions do not appear to cause serious pericardial injury, they may involve a degree of disruption to the serosal lining that could become significant when other factors are taken into account.

Recently, Marsa et al.[8] described 3 cases of constrictive pericarditis after cardiac surgery in which it was believed that a povidone-iodine pericardial irrigating solution was a major factor. Our current study demonstrates a definite cluster of 5 cases (Patients 4 to 8) that occurred during the time when a povidone-iodine irrigant solution was used. Ironically, povidone-iodine by itself has very little tissue toxicity and has demonstrated low irritability in open wounds.[24,25] However, combined with factors such as hemorrhage, air-drying and cold injury, it may seriously irritate the serosal lining of the pericardium. In view of this, it may be wise to avoid pericardial irrigating solutions that include povidone-iodine. All 3 patients who responded to medical therapy (Patients 3, 9, and 10) had pericardial irrigation with normal saline solution. It is possible that this may be a significant modifier in the degree of pericardial irritation and subsequent development of irreversible rigid fibrous constriction.

In summary, the pathophysiologic process of constriction in an open pericardium is multifactorial. Irritation of the pericardial layers, both by iced saline solution during cardiopulmonary bypass and by irrigating solutions before chest closure, and postoperative hemorrhage and pooling of blood in the posterior pericardium, appear to be major events. The combination of these factors may initiate inflammation, adhesions, fibrosis and resultant degrees of pericardial constriction with or without effusion.

Clinical aspects: There does not appear to be a clear indicator to predict which patients will have constrictive pericarditis after cardiac surgery. Although 5 of our 11 patients had early postoperative pericarditis that required treatment, this condition does not appear to cause the constrictive disease. Some degree of pericarditis is present in nearly all patients after cardiac surgery, and symptomatic pericarditis requiring therapy occurs in 15 to 30 percent of patients.[2]

The symptoms and signs of postoperative constriction are similar to those of classic chronic constriction

as described by Wood.[26] Postoperative constriction in this study manifested itself an average of 2 to 3 months after cardiac surgery. This time frame is earlier than expected for the development of a true chronic rigid fibrosis but may suggest the evolution of a more elastic type of constrictive process with a possible element of seroeffusion. Cases presenting earlier than 2 months may represent a variation of late tamponade or subacute effusive pericarditis.

M mode echocardiography is helpful in the noninvasive evaluation of constriction after cardiac surgery, but it is not clearly diagnostic considering the usual abnormalities of septal motion after such surgery and the lack of a definitive pattern in constrictive pericarditis unrelated to surgery.[27] Nevertheless, the presence of marked pericardial thickening or a posterior pericardial effusion, or both, raises the index of suspicion for postoperative constriction.

The most reliable diagnostic test to document constriction after cardiac surgery was right and left heart catheterization. The basic hemodynamic patterns of this entity are similar to the classic constrictive hemodynamics defined by Shabetai et al.[28] In some cases, the variable degrees of dominant x and y descents in the pressure tracing and the contour of the right ventricular and left ventricular early diastolic dip suggest a less rigid form of constriction similar to Hancock's fibroelastic or seroeffusive constriction,[13,14] although modified by factors of an open pericardium and previous surgery.

Therapy: A degree of caution should be instituted when clinical data point to constrictive pericarditis after cardiac surgery. Restrictive cardiomyopathy may easily mimic pericardial constriction.[29] The differentiation between the two is often difficult and sometimes may only be resolved by surgical evaluation. Nevertheless, if enough evidence is present to suspect pericardial constriction, aggressive and definitive therapy should be implemented.

Unless contraindicated, an initial medical regimen of diuretic drugs and steroids or anti-inflammatory agents seems warranted. Diuretic drugs may facilitate resorption of fluid in the pericardial space and steroids may reduce the inflammatory response. A response to this therapy may indicate a reversible seroeffusive variation of constrictive pericarditis. The patient should be evaluated frequently and, if symptoms and signs do not recur, therapy should gradually be tapered and discontinued if possible.

If the patient fails to respond to medical therapy and constrictive findings persist, surgical intervention is indicated. If pathologic findings of constrictive pericarditis are found, a radical pericardiectomy should be performed. Although this is an extensive operation, great care should be taken to remove completely the parietal and visceral pericardium.[30,31] and evacuate any loculated hematoma to obtain optimal benefits.

Conclusions: Contrary to previous beliefs, constrictive pericarditis may develop as a complication of cardiac surgery despite an open pericardium. In this study, the incidence rate was 0.2%. Certain clinical and hemodynamic aspects of this entity suggest an elastic form of constriction with reversible and irreversible elements. The development of pericardial constriction after cardiac surgery is not a single pathophysiologic model, but represents a wide clinical spectrum with variable therapeutic responses. Constrictive pericarditis should be considered in the differential diagnosis of patients who, after cardiac surgery, present with cardiac decompensation dominated by right-sided symptoms and signs.

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Increased Physical Activity: A Protective Factor Against Heart Attacks in Puerto Rico

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The incidence and potential risk factors of coronary heart disease were assessed in 2,585 rural and 6,208 urban men, aged 45 to 64 years, participating in the Puerto Rico Heart Health Program, a prospective epidemiologic study of coronary heart disease initiated in 1965. An index of daily physical activity and a metabolic equivalent of heaviest activity were estimated from each individual history. Rural men had higher mean levels of overall activity as well as higher levels of heavy activity than urban men. An 8¼ year follow-up study for coronary heart disease other than angina pectoris was analyzed for relationships with physical activity. Significant inverse associations were found for both urban and rural men. Metabolic equivalent of heaviest activity showed similar results. Although the physical activity index was inversely associated with most known coronary risk factors, multivariate analyses indicated that a significant independent inverse relationship existed with the incidence of coronary heart disease. In Puerto Rico, increased physical activity appears to be a separate protective factor against heart attacks.

The status of physical activity as a protective factor against coronary heart disease continues to be evaluated by epidemiologists and clinical investigators. A recent report from Framingham[1] suggests an inverse relationship between usual physical activity assessed at baseline and the subsequent development of coronary heart disease within 14 years. In contrast to the mainland United States, where a sedentary life-style is almost universal, rural Puerto Ricans are much more involved in regular physical activity. This higher activity level in rural men very likely represents occupation-related activities such as farming and cutting sugar cane. Furthermore, in the hilly rural area where access to roads is limited, the daily activities of living require a considerable amount of strenuous walking. This situation provides more variability in exercise level within a population and has analytical advantages.

The Puerto Rico Heart Health Program originated in 1965 and has followed up a group of 8,793 men, aged 45 to 64 years, for incidence of coronary heart disease.[2] An early report from this study,[3] with 2½ years of follow-up, gave equivocal results as to the importance of physical activity as a predictor of subsequent coronary heart disease. The availability of 8¼ years of follow-up data provides a better opportunity for a detailed analysis of this important question.

Methods

Study group: The Puerto Rico Heart Health Program is a prospective epidemiologic study of coronary heart disease in urban and rural men aged 45 to 64 years when determined in 1965.[2] An enumeration of all men of these ages living in 3 urban and 4 rural areas in the northeast part of Puerto Rico was conducted by the personnel who participated in the United States decennial census. The urban group consisted of those areas in 3 *municipios* (municipalities) in the metropolitan area of San Juan with housing clusters of 25 or more dwelling units. The rural group consisted of the hilly farming

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TABLE I Mean Values and Standard Deviations (SD) of Physical Activity Index and Metabolic Equivalent of Heaviest Activity in Men Aged 45 to 64 Years at Examination 1; Puerto Rico Heart Health Program

Area and Age (yr)	Physical Activity Index			Metabolic Equivalent		
	Mean	SD	n	Mean	SD	n
Rural						
45–49	39.2	11.0	560	6.28	2.11	557
50–54	38.7	10.9	738	6.22	2.10	736
55–59	37.9	10.5	683	6.15	2.13	679
60–64	36.7	10.2	597	6.23	2.02	597
	Unknown physical activity		7	Unknown metabolic equivalent		16
Total			2,585			2,585
Urban						
45–49	31.5	6.9	1,682	4.57	2.01	1,681
50–54	31.3	6.4	1,930	4.63	2.04	1,937
55–59	31.5	6.6	1,425	4.69	2.04	1,426
60–64	30.5	6.4	1,142	4.39	1.89	1,143
	Unknown physical activity		29	Unknown metabolic equivalent		21
Total			6,208			6,208

areas of 4 *municipios* located up to 35 miles from San Juan. All of these men were encouraged to attend the baseline examination, and an 80% response rate was achieved. At examination, men of other ages (35 to 44 and 65 to 79 years) who had been inappropriately included in the enumeration were accepted, and the total number of examined men was 9,824.

At the initial examination, each participant provided sociodemographic information and a medical history and had a physical examination with laboratory determinations and a resting 12-lead electrocardiogram. At this 1st examination, 2,585 rural and 6,208 urban men aged 45 to 64 years were assessed for physical activity status. Only 36 had an incomplete history. All persons were evaluated with cardiovascular examinations at 3 subsequent periods, the last being 8¼ years from the initial examination. Participation in the reexamination included about 90% of survivors, and those not appearing for examination were followed up for vital status. Diagnosis of coronary heart disease was made according to predetermined criteria.[2] For example, criteria for myocardial infarction included prolonged chest pain and pathologic Q waves or evidence of muscle necrosis by enzyme studies, or both. The classification of coronary disease other than angina pectoris (heart attacks) included sudden and nonsudden coronary heart disease death, myocardial infarction, and coronary insufficiency, but not angina pectoris.

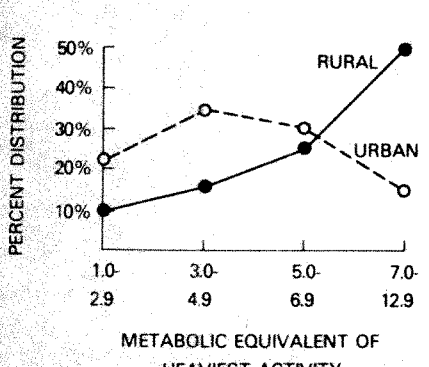


FIGURE 1. Percent distribution of metabolic equivalent of heaviest activity, by area, in men aged 45 to 64 in the Puerto Rico Heart Program.

At the initial examination and subsequently at 2 follow-up examinations, usual 24 hour physical activity was assessed. The number of hours of rest and sleep as well as of occupational, leisure, and other activities were ascertained. These activities were classified as sedentary, slight, moderate, and heavy. A weighting factor for each level of effort was multiplied by the number of hours engaged in the activity, and these were added to give a physical activity index. The weighting factors for sleep and for sedentary, slight, moderate, and heavy activity were 1.0, 1.1, 1.5, 2.4, and 5.0, respectively.[2] The questionnaire and the weighting factors were patterned after those of the Framingham Study. The weighting factors somewhat approximate the oxygen consumption for each of these activities.[1]

In addition, each individual was asked to identify the heaviest activity lasting at least 2 hours per week. A set of metabolic equivalents derived from the literature[4] was applied to these occupational or leisure time activities. The metabolic equivalent is the ratio between energy expenditure of the activity and the basal state. The heaviest activity was then characterized by this metabolic equivalent.

Statistical analysis: The logistic function model was used to analyze the relationships between physical activity and the clinically manifest incidence of coronary heart disease for univariate and multivariate situations, and coefficients were estimated by the maximal likelihood method.[5] If the ratio (z) between the regression coefficient and its standard error is greater than 1.96, the coefficient is statistically significant at the $p < 0.05$ level.

Results

Physical activity and metabolic equivalent indexes: As a measure of the repeatability of the assessment of physical activity, between-examination correlation coefficients of the indexes were calculated. Physical activity was measured at 3 successive examinations 2½ to 3 years apart. The physical activity correlations are between 0.30 and 0.59 depending on the area and examination pair. For comparison, except for fairly stable measurements such as height and weight,

TABLE II Correlation Among Physical Activity Index and Specified Variables at Examination 1 in Men Aged 45 to 64 Years Free of Coronary Heart Disease; Puerto Rico Heart Health Program

	Rural		Urban	
	Age 45–54	Age 55–64	Age 45–54	Age 55–64
Systolic blood pressure (mm Hg)	−0.09	−0.09	−0.06	−0.06
Diastolic blood pressure (mm Hg)	−0.13	−0.11	−0.08	−0.06
Heart rate (beats/min)	−0.17	−0.21	−0.11	−0.15
Cigarettes per day (n)	−0.03	−0.03	−0.00	0.04
Blood glucose (mg/dl)	−0.07	−0.05	−0.06	−0.07
Hematocrit (%)	−0.08	−0.01	−0.04	−0.05
Fasting serum triglycerides (mg/dl)	−0.08	−0.17	−0.08	−0.07
Monthly income ($)	−0.14	−0.03	−0.06	−0.06
Vital capacity (liters)	0.08	0.07	0.02	0.01
Relative weight (%)	−0.15	−0.05	−0.09	−0.10
Serum cholesterol (mg/dl)	0.01	−0.08	−0.02	−0.02
Total calories (cal)	0.03	0.18	0.03	0.06
Total carbohydrates (g)	0.12	0.18	0.08	0.08
Alcohol (g)	−0.04	0.08	−0.01	0.02
Men (n)	1,161	1,105	3,237	2,227
Fasting men (n)	757	729	2,027	1,417

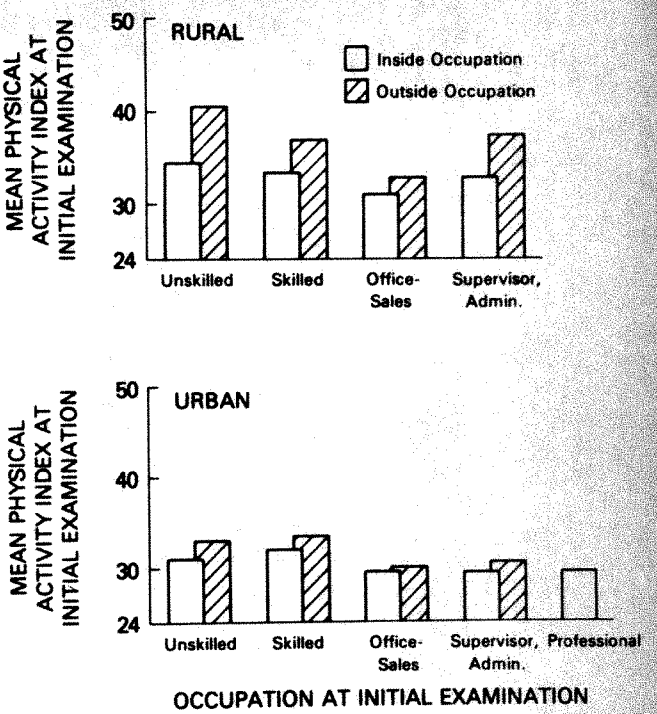


FIGURE 2. Age-adjusted mean value of physical activity by levels of occupation, in men aged 45 to 64 years free of coronary heart disease.

the between-examination correlation of systolic blood pressure is among the largest obtained and ranges from 0.64 to 0.72. Although the reliability of physical activity assessment is of concern, the between-examination correlations suggest reproducibility from 1 examination to the next. The between-examination correlations of metabolic equivalent are similar to those of the physical activity index. Although physical activity assessment addresses usual overall activity and the metabolic equivalent addresses heaviest activity, these 2 indexes are highly correlated with each other (r = 0.63 for rural; r = 0.55 for urban).

The mean values of physical activity differ considerably by age and area of residence (Table I). The residents of rural areas have higher average levels of physical activity index and metabolic equivalent of highest activity than do urban subjects. There is a slight trend toward less physical activity in the older subjects.

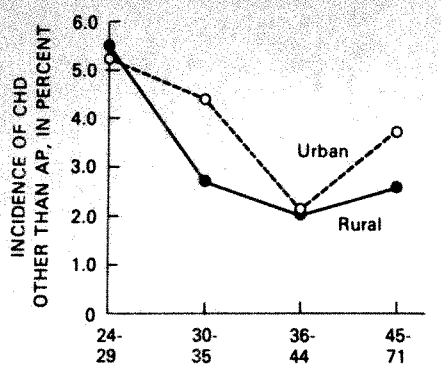
The distribution of metabolic equivalent of heaviest activity (metabolic equivalent) (Fig. 1) shows that almost 50% of the men in the rural area have a metabolic equivalent level of 7 or more. This figure indicates that they engage in an activity of at least metabolic equivalent 7 for a total of at least 2 hours a week. A level of 7 or more can be achieved by activities such as moving heavy objects of 30 kg (65 pounds) or more, shoveling, or cutting sugar cane.

Physical activity index shows a relationship with occupational classification, particularly in rural areas (Fig. 2). Persons whose principal job location is out-of-doors show higher mean levels of activity than do those with indoor occupations.

Unskilled and skilled workers show higher levels than do those with more sedentary occupations such as office work. The high level of physical activity in the rural supervisor class, that is, the owner of a farm, is worth noting. Although he may not directly work the farm, he may be involved in a variety of activities, such as walking or climbing hills to supervise his workers, which would result in a higher index. These expected associations with occupation add credibility to the use of the physical activity index as a measure of activity.

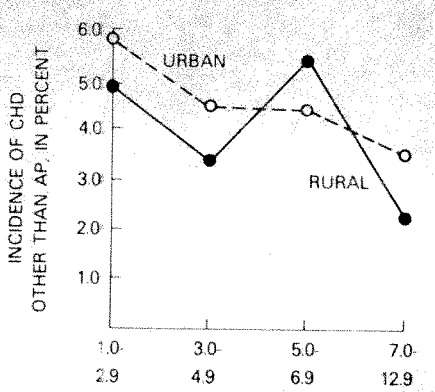
Association with other factors: Product moment correlation coefficients were calculated between physical activity index and a variety of other characteristics measured at the initial examination (Table II). Heart rate stands out as the variable most strongly correlated with physical activity. The sign is negative, indicating that greater physical activity is associated with decreased heart rate. It also provides credibility of the physical activity index as a measure of physical activity because the hallmark of a cardiovascular response to physical training is resting bradycardia. As further confirmation of the higher exercise levels in this population, 23.4% of the rural and 10.7% of the urban men have a resting heart rate below 60 beats/min. In general, physical activity correlates in a beneficial way with most of the usual risk factors for coronary heart disease. A higher physical activity index is associated with decreased blood pressure, relative weight, and serum cholesterol level; however, these correlations are generally small.

Relationship with coronary heart disease: Physical activity is inversely associated with the 8¼ year incidence of coronary heart disease other than angina pectoris (Fig. 3). This association is statistically dif-



POPULATION:				
URBAN	3,404	1,403	641	354
RURAL	753	440	539	687

FIGURE 3. Incidence of coronary heart disease (CHD) other than angina pectoris (AP) by physical activity index; age-adjusted 8¼ year rates in men aged 45 to 64 years.



POPULATION:				
URBAN	1,297	1,998	1,716	798
RURAL	234	386	604	1,186

FIGURE 4. Incidence of coronary heart disease (CHD) other than angina pectoris (AP) by metabolic equivalent of heaviest activity; age-adjusted 8¼ year rates, in men aged 45 to 64 years.

ferent from zero and shows that the highest incidence of coronary heart disease, other than angina pectoris, is found in men in the lowest physical activity group. A point of minimal risk appears at level 36 to 44 and a slight increase in risk at highest level of physical activity. The range of risk is twofold from the lowest to the highest. The index of 36 to 44 could be approximated by the sum of 8 hours of sleep, 8 hours of sitting, and 8 hours of walking. The population at risk indicates that there are adequate numbers at each level of activity, and these numbers are slightly lower than the totals found in Table I, because the population at risk is free of existing coronary heart disease.

Physical activity is not related to the incidence of angina pectoris (Table III). Age-adjusted standardized logistic function coefficients show no apparent significant relationship for angina pectoris. The coefficients for coronary heart disease other than angina pectoris are statistically significant, with a lower incidence in the physically active group.

Incidence of coronary heart disease other than angina pectoris is also associated with the metabolic equivalent (Fig. 4). This figure does not show the upturn in incidence for those who engage in very heavy activities, although a slight increase is observed in the next lower group. Using the logistic function, the age-adjusted trends for rural and urban groups are statistically significant.

The activity index used in this study is a composite of the number of hours spent at varying levels of activity. It is of interest whether any specific activity is associated with the risk of coronary heart disease. Because the number of hours of sleep and sedentary, slight, moderate, and heavy activity must add up to 24, these activities are correlated with each other. The number of hours of sleep and sedentary activity are negatively correlated with the amount of moderate and heavy activity. The association of the number of hours of each activity with coronary heart disease other than angina pectoris is shown in Table IV. Increased duration of sleep is associated with a higher incidence of coronary heart disease other than angina pectoris, whereas higher levels of moderate and heavy activity are associated with a lower incidence.

Correcting for related factors: Multivariate analysis attempts to determine whether the observed association is merely a result of the association of physical activity with other known risk factors. The coefficients of the multiple logistic function are shown in Table V. Even when the other specified factors are taken into account, physical activity contributes independently to the risk of coronary heart disease other than angina pectoris. When both the hours of sleep and hours of heavy activity are entered simultaneously into the multivariate equation and the physical activity index is removed, neither of these 2 components reach independent significance. This finding suggests that the physical activity index, which is the weighted sum of different activity levels, is more closely associated with coronary heart disease than with any of the separate activity levels themselves.

One factor that may be a confounding variable and that cannot be quantified adequately, is coexisting disease; for example, is low physical activity an individual's response to existing ill health rather than a promoter of poor cardiovascular health? The analysis of incidence in this report was calculated for a period of 8¼ years and used a base population free of definite or questionable clinically evident coronary heart disease. Thus, at the time of assessment of physical activity, the population analyzed did not have clinically recognized coronary disease. Additionally, the analysis in Table V was made excluding events in the first 2½ years after the

TABLE III Standardized Logistic Function Coefficients of Specified Coronary Heart Disease Events on Physical Activity Index Age-Adjusted for Men 45 to 64 Years; Puerto Rico Heart Health Program, 8¼ Year Follow-Up Study

Event	Rural		Urban	
	Coefficient	z*	Coefficient	z*
Coronary heart disease other than angina pectoris	−0.353	−2.72	−0.223	−2.79
Angina pectoris	0.192	1.37	0.036	0.37

* A z score greater than 1.96 is equivalent to a p value less than 0.05.

TABLE IV Standardized Age-Adjusted Coefficients of Coronary Heart Disease Other Than Angina Pectoris on Components of Physical Activity in Men Aged 45 to 64 Years; Puerto Rico Heart Health Program, 8¼ Year Follow-Up Study

Number of Hours of:	Rural		Urban	
	Coefficient	z	Coefficient	z
Sleep	0.278	3.02	0.096	1.63
Sedentary activity	0.083	0.74	0.114	1.77
Slight activity	0.066	0.61	0.008	0.12
Moderate activity	−0.144	−1.19	−0.255	−3.19
Heavy activity	−0.312	−2.34	−0.145	−1.86

physical activity measurement. By excluding these early cases, we most likely eliminated those individuals whose low level of physical activity could have been a response to serious ill health, leaving the remaining cases less affected by this phenomenon. The results were essentially the same, although in the urban area the slope for physical activity was slightly lower. There is a significant independent association (inverse) between physical activity index and incidence of coronary heart disease other than angina pectoris, indicating that existing disease may be partly, but not completely, responsible for the observed association.

Discussion

Comparison with the Framingham Study: Findings from an 8¼ year follow-up study of the Puerto Rico cohort are generally consistent with those of other reported epidemiologic studies.[6–11] A significant inverse multivariate relationship was found in the prospectively studied Framingham population.[1] Although the same physical activity questionnaire was used in both locations, no strict comparative studies were performed. Nevertheless, the mean levels in Framingham and urban Puerto Rico are similar, whereas, as expected, the rural Puerto Rican men have higher activity scores. When the relative magnitude of standardized multivariate logistic coefficients in the 2 studies is compared, physical activity index in Framingham is 5th behind systolic blood pressure, cholesterol, cigarettes, and age.

TABLE V Multiple Logistic Function Coefficients: Risk of Coronary Heart Disease Other Than Angina Pectoris Men Aged 45 to 64 Years; Puerto Rico Heart Health Program, 8¼ Year Follow-Up Study

Independent Variables	Standardized Multiple Coefficients			
	Rural		Urban	
	Coefficient	z Statistic	Coefficient	z Statistic
Age	0.125	1.04	0.131	1.98
Physical activity index	−0.273	−2.03	−0.181	−2.30
Systolic blood pressure	0.519	5.45	0.411	7.28
Relative weight	−0.068	−0.60	0.057	0.86
Cigarettes smoked	0.182	1.75	0.120	2.03
Heart rate	0.024	0.22	0.013	0.20
Serum cholesterol	0.114	1.05	0.252	4.48
Cases (n)/cases at risk (n)	81/2,389		254/5,766	

Among rural Puerto Rican men, the physical activity index is 2nd behind only blood pressure in predicting subsequent heart attack. This finding suggests that in a low-incidence setting where there is a wider range of physical activity, increased physical activity may have more detectable effects. The relative risk, approximated by relative odds, for a 10 unit difference in physical activity index is about 1.3 in rural Puerto Rico, a value comparable to that found in Framingham.

Comparison with other studies: In at least 3 other United States populations[12–14] and in Sweden,[15] a consistent relationship with physical activity was not detected. These studies primarily used estimates of physical activity associated with occupation. Other occupation-based studies, including those of busmen[6] and longshoremen,[9] show a relationship. It is possible that in certain industrial situations, the difference in job-related activity is minimal, and greatest variation is found in leisure time activities. In a Belgian study, gardening, cycling, and walking on a regular basis were protective factors against coronary heart disease.[16] In a case-control retrospective study, leisure activity was more protective against death than was job-related activity. In the Puerto Rico study leisure activities were not separated from occupational activities in the final estimate of the physical activity index or metabolic equivalent of maximal 2 hour effort.

In the Puerto Rico study there was no threshold of physical activity at which the incidence of coronary attacks increased abruptly. The existence of such a critical level has been hypothesized.[17] However, above a score of 44, there was a slight upturn in incidence, resulting in some suggestion of a J-shaped relationship (Fig. 3).

The increased incidence of coronary attacks among those urban men with an index above 44 may be confounded with cigarette smoking. When the data for Figure 3 were analyzed for cigarette smokers and nonsmokers separately, a steady decreasing incidence with increased activity was seen for nonsmokers. Cigarette

smokers showed a decreasing incidence until level 45 to 71, where the incidence increased to the same level as that of the least physically active group. Although this result should be viewed with caution because of the small number of active urban men, the implication is that high physical activity is not as beneficial in cigarette smokers. There have been a few reports[18] of occupations with high intensity activity being associated with increased cardiovascular risk.

Physical activity and coronary atherosclerosis: Some investigations, however, suggest that physical activity may contribute more to preventing death, especially sudden death, than having an effect on total incidence through decreasing the amount of atherosclerosis.[9] In Puerto Rico, the relationship is similar whether heart attacks or coronary heart disease deaths are used separately as end points. The percentage of fatal heart attacks is comparable for those with high or low levels of physical activity. Too few sudden deaths have occurred in this cohort to permit meaningful analysis.

Autopsy series, although potentially biased in unknown ways, provide some additional information. No relationship between physical activity and mural atherosclerosis was found by Morris and Crawford,[19] although a relationship did exist between coronary occlusion and the number of myocardial lesions. Spain and Bradess,[20] using information concerning premortem occupation, found an apparent inverse relationship between the degree of atherosclerosis and the level of physical activity. Autopsy results from the Puerto Rico study show a trend, although nonsignificant, towards a relationship between greater levels of physical activity and decreased coronary atherosclerosis.[21]

Assessment of physical activity: The measurement tool used in this study was developed by Framingham Heart Study personnel. It suffers from the potential problem of both the interviewer's bias entering into the final scoring of the index and the inaccurate recall by the subject. Other sensitive, detailed, and potentially more accurate instruments have been developed after the start of the Puerto Rico Study.[22] In this study, an additional measure of physical activity was used, namely, the metabolic equivalent of the most intense activity. This value is strongly correlated with the physical activity index, and not surprisingly, results are similar with both measures of physical activity.

To differentiate the important components of physical activity under the separate effects of basal activities of sleep and rest versus heavy levels of activity, both of these activities were entered simultaneously into a multivariate logistic calculation. In this situation, neither component of activity was strongly significant, suggesting that it was the interrelated blend of activities that was most important.

Cause or effect: A recurrent concern among investigators considering the physical activity question is the potential problem of differentiating between selective factors and protective ones. After the first study of Morris et al.,[23] they investigated this aspect in a unique way[6] and found that although selective factors may have been operating, with obese persons choosing the driver jobs more often, they could not explain the entire difference between conductors and bus drivers. In prospective studies using a questionnaire representing current activities, the preclinically identified cardiac patient may reduce his activity. All participants in the present analysis were free of clinically recognized coronary disease at baseline, and the incidence was evaluated over the next 8¼ years. In a further attempt to eliminate any bias, the incidence cases in the first 2½ years of experience were eliminated. The relationship held, although some of the association was presumably accounted for by unknown coronary disease.

Other factors: An attempt was made in the analysis to correct for the other known correlates of physical activity that are potential risk factors for coronary heart disease. Blood pressure, cigarette smoking, cholesterol, heart rate, and relative weight were included in the multivariate analysis, and physical activity remained statistically significant. High density lipoprotein cholesterol, which appears to be elevated with physical activity,[24] was measured only in a pilot study; and platelet stickiness, fibrinolysins, and other hematologic factors were not measured in this study. In addition, no direct measures of emotional "stress" were made in this population. If occupational class is considered as a rough measure of possible increased job pressure, physical activity has a comparable inverse relationship with the incidence of heart attack in each of the occupational categories. Therefore, it is doubtful that our results can be explained in a bias due to "stress" being greater and physical activity being less in 1 subgroup compared with another.

Implications: The notion that physical activity may be protective against heart attacks has gained in popularity, and has resulted in recommendations, using mass media, to get people interested in exercise, group and personal incentives to maintain interest, and the provision of special places to exercise.[25] This physical activity hypothesis, however, has not been adequately tested with appropriate clinical trials.[26]

The Puerto Rico study, a prospective epidemiologic investigation, supports previous studies that increased physical activity may protect against coronary heart disease. This observation has been extended to a low incidence area, where the rate of heart attacks is about half that of the mainland. The benefits from the higher activity levels in Puerto Rico probably reflect a lifetime pattern of steady activity rather than a recent increase in exercise.

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Inter- and Intraatrial Dissociation During Spontaneous Atrial Flutter: Evidence for a Focal Origin of the Arrhythmia

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Programmed electrical stimulation of the heart was performed in 2 patients with spontaneous atrial flutter. Patient 1 was a young man with paroxysmal atrial flutter that had proved resistant to drug therapy and who was studied during an episode of sustained flutter. In this patient rapid atrial pacing from the coronary sinus at a critical rate faster than the intrinsic flutter rate provoked local atrial fibrillation in the mid and low right atrium which persisted after termination of pacing. In spite of persistent local fibrillation in these regions, atrial flutter continued in the left atrium and the high right atrium. A second burst of pacing resulted in restoration of sinus rhythm. Patient 2 was an elderly woman with probable sick sinus syndrome who developed spontaneous atrial flutter during the course of an electrophysiologic investigation. During flutter intracavitary recordings from multiple sites in the atria revealed a pattern of 3:2 Wenckebach conduction between the left atrium and the high right atrium, with block of every third atrial depolarization at the latter site. These results indicate that atrial flutter may exist at some sites in the atria which are functionally dissociated from the remainder of the atrial tissue, thus supporting the hypothesis that flutter in some patients may be focal in origin.

The electrophysiologic mechanism of atrial flutter in human beings has long been a matter of controversy. Some authors[1,2] have suggested that atrial flutter is due to circus movement which incorporates a large mass of atrial myocardium. An opposing view is that atrial flutter is basically focal in origin, arising in a small functionally circumscribed area of tissue.[3–5] Recently, utilizing programmed electrical stimulation of the heart, we had the opportunity to study 2 patients with spontaneous atrial flutter in whom flutter existed in a part of the atria functionally dissociated from adjacent areas. Since these observations suggest a focal origin of the arrhythmia, we report the results obtained in these patients in detail.

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Methods

Patients: Patient 1 is a 30 year old man with no demonstrable structural heart disease who first developed paroxysmal atrial flutter 2 years earlier. Despite therapy with digoxin, quinidine sulfate, disopyramide phosphate, and amiodarone, either singly or in combination, the paroxysms of atrial flutter continued, culminating in an episode of sustained atrial flutter which required hospital admission.

Patient 2 is a 71 year old woman with a history of mild hypertension, stable angina pectoris, and sick sinus syndrome, characterized by periods of sinus bradycardia alternating with paroxysmal atrial fibrillation and supraventricular tachycardia. Because of excerbation of angina during tachycardia and at least 1 syncopal episode, she was referred to our hospital for further evaluation.

Electrophysiologic study: Both patients underwent electrophysiologic investigation in the postabsorptive, nonsedated state. Patient 1 was receiving amiodarone, 400 mg by mouth daily, at the time of study. Patient 2 had had no antiarrhythmic drugs for 24 hours before the study. After in-

formed consent was obtained, the patients were taken to the cardiac catheterization laboratory where, using the Seldinger technique, electrode catheters were passed through both femoral veins and positioned in the heart under fluoroscopic guidance. These included quadripolar catheters in the right atrium and coronary sinus, a bipolar catheter in the right ventricular apex, and a bipolar catheter placed across the tricuspid valve for recording the His bundle electrogram.

The methods for stimulation and recording used in our laboratory have previously been described in detail.[6] In brief, in the presence of sinus rhythm refractory periods were determined using the single test stimulus method during basic drive pacing of the atrium and ventricle at each of several basic cycle lengths. During atrial flutter the effects of single or multiple atrial premature depolarizations on the time relations of the tachycardia were studied first. This was followed by bursts of rapid atrial pacing at progressively decreasing pacing cycle lengths in an attempt to terminate tachycardia. In addition, Patient 2 received an infusion of procainamide, 600 mg intravenously over 6 minutes, in order to study the drug's effectiveness in terminating flutter.

Results

Patient 1

Atrial recordings during flutter (Fig. 1): Atrial flutter with a 4:1 A-V relationship was present at the beginning of the electrophysiologic investigation. The flutter waves in the inferior electrocardiographic leads demonstrated an initial negative followed by a positive deflection as in flutter of the so-called common type. Examination of bipolar atrial electrograms from multiple sites revealed an atrial rate of 260/min (cycle length 230 ms) that varied slightly, the minimum and maximum cycle lengths being 220 and 250 ms, respectively. Earliest atrial activity was present in the low right atrial septum in the region of the His bundle recording site and corresponded to the beginning of the flutter waves in the surface electrocardiogram. Atrial activity next appeared in the proximal coronary sinus, followed by nearly simultaneous activation in the distal coronary sinus as well as the high and mid right atrium (high right atrium not shown). The atrial electrogram recorded from the mid right atrium appeared somewhat broad and fragmented in comparison with the sharper, more discrete electrograms recorded at other sites. However, at all sites the recordings between successive electrograms were isoelectric, without any evidence of continuous electrical activity (Fig. 1).

Single atrial extrastimuli were ineffective in terminating atrial flutter, regardless of their degree of prematurity or the site at which they were delivered. These extrastimuli either evoked no response or were followed by only local early depolarization and then a fully compensatory pause. Depolarization at other more distant sites occurred when expected, the flutter continuing at the same rate and with the same atrial activation sequence. Similarly, 2 or 3 consecutive atrial extrastimuli did not interrupt or alter the arrhythmia.

Rapid atrial pacing (Fig. 2): During rapid atrial pacing at rates slightly faster than the flutter rate (cycle length 170 to 200 ms), all atrial recording sites were depolarized at the pacing rate and the atrial activation sequence was different from that during flutter, earliest activity now occurring in the distal coronary sinus (near the pacing site), followed by the His bundle region and then the high and mid right atrium nearly simultaneously. This was reflected in the surface electrocardiogram by flutter waves of lower amplitude which had a small initial positive component. The atrial electrograms in the mid right atrium and His bundle region during pacing at these rates appeared broader and more fragmented than during atrial flutter. When the pacing train of stimuli was stopped, atrial flutter reappeared in the first postpacing cycle. The atrial activation sequence and flutter rate after pacing at these rates were identical to those before the pacing train. During atrial pacing at a more rapid rate (cycle length 160 ms) the atrial electrograms recorded in the mid right atrium and His bundle region demonstrated irregular, continuous electrical activity spanning the entire interval between pacing

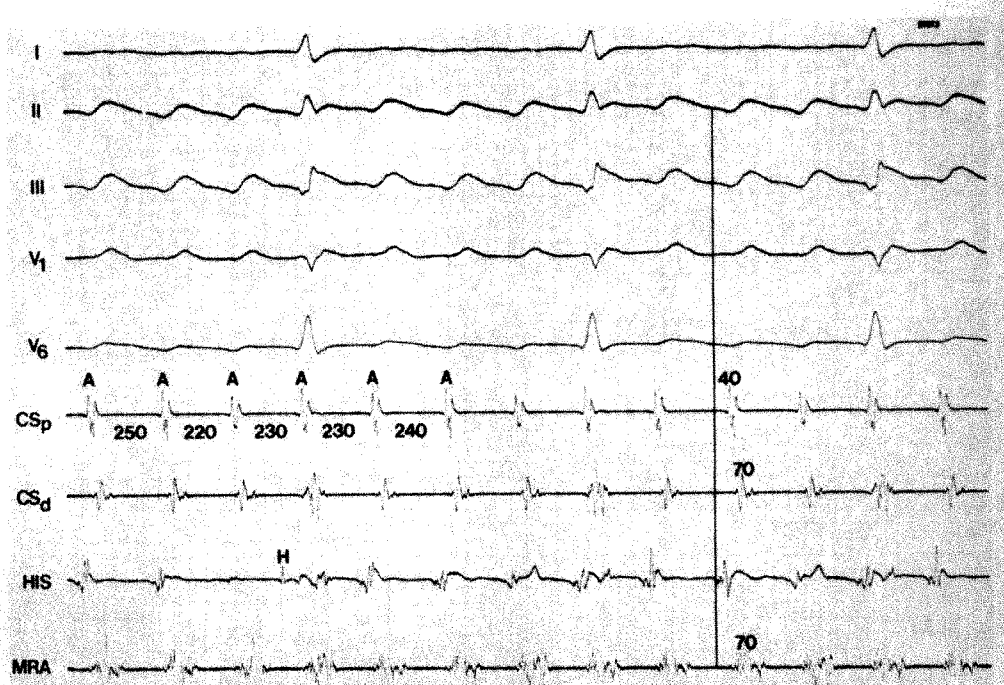

FIGURE 1. Patient 1. Simultaneous recording of **(top to bottom)** electrocardiographic leads I, II, III, V_1, and V_6, as well as electrograms from the proximal coronary sinus (CS_p), distal coronary sinus (CS_d), His bundle region, and mid right atrium (MRA) during spontaneous atrial flutter. The atrial cycle length varies between 220 and 250 ms. **Vertical line at right** marks the beginning of the flutter wave in lead II with corresponding activation times at each atrial recording site as indicated. Earliest atrial activity appears in the His bundle recording site. Note the stable isoelectric baseline between successive atrial electrograms at each recording site.

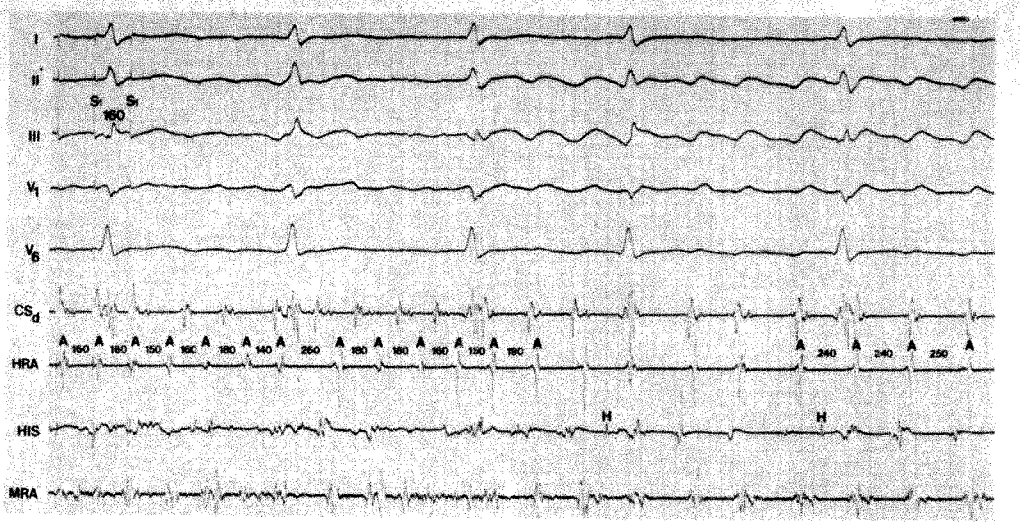

FIGURE 2. Patient 1. Simultaneous recording of (**top to bottom**) electrocardiographic leads I, II, III, V_1 and V_6, as well as electrograms from the distal coronary sinus (CS_d), high right atrium (HRA), His bundle region, and mid-right atrium (MRA) during and immediately after a burst of pacing from the coronary sinus at a cycle length (S_1–S_1) of 160 ms. The last 3 paced beats of the pacing train are shown on the **left**. After termination of pacing there is fragmented, continuous electrical activity in His bundle region and mid-right atrium. Atrial electrograms at the other 2 sites remain discrete, with isoelectric baselines separating successive atrial deflections. Immediately after pacing there is transient overdrive acceleration of flutter, as determined by the rate of depolarization in the coronary sinus and high right atrium. As local fibrillation in the mid-right atrium and His bundle recording sites disappears, the rate of flutter returns to that present before pacing.

stimuli, consistent with local fibrillation. In contrast, electrograms from the high right atrium and distal coronary sinus continued to show regular, discrete deflections after each pacing stimulus. After termination of pacing at this rate, transient overdrive acceleration of flutter was noted, manifested by repetitive, discrete, slightly irregular, flutter-like electrograms in the high right atrium and distal coronary sinus at a rate faster than the intrinsic flutter rate before pacing. The continuous electrical activity recorded in the mid right atrium and His bundle region also persisted transiently after pacing. The surface electrocardiogram at this time did not show discrete flutter waves, but instead resembled typical atrial fibrillation. Gradually, the continuous electrical activity in the mid and low right atrium became more organized; this was associated with slowing of the flutter rate back to the intrinsic rate present before pacing and the reappearance of typical flutter waves.

During a 15 second burst of atrial pacing at a cycle length of 150 ms (Fig. 3), similar observations were made as during pacing at a cycle length of 160 ms. However, after this burst overdrive acceleration in the distal coronary sinus and high right atrium was persistent rather than transient, accompanied by persistent continuous electrical activity in the mid- and low right atrium as well as the electrocardiographic appearance of atrial fibrillation. After several minutes of this persistent overdrive acceleration, a second burst of atrial

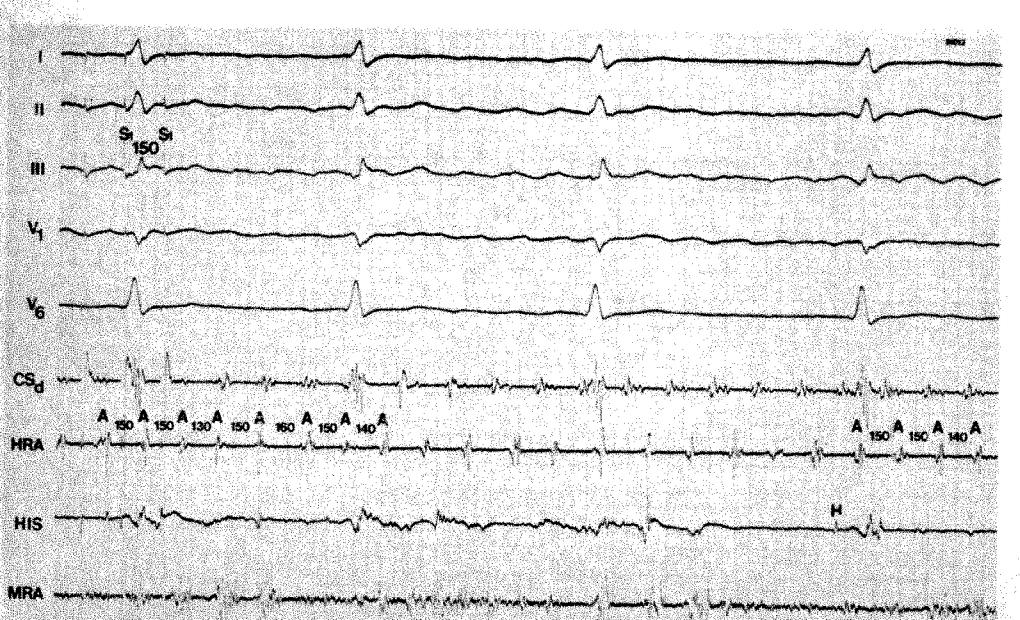

FIGURE 3. Patient 1. Same organizations of tracings as in Figure 2 during the rhythm immediately after a burst of atrial pacing from the distal coronary sinus (CS_d) at a cycle length (S_1–S_1) of 150 ms. The last 3 paced beats of the pacing train are shown on the **left.** Continuous, fragmented electrical activity is present in the mid right atrium (MRA) and His bundle region during pacing and persists after termination of pacing. This is associated with persistent postpacing overdrive acceleration of flutter in the high right atrium (HRA) and coronary sinus. This overdrive acceleration of flutter was still present 2 minutes after termination of pacing. Note the appearance of atrial fibrillation in the surface electrocardiogram after pacing has stopped.

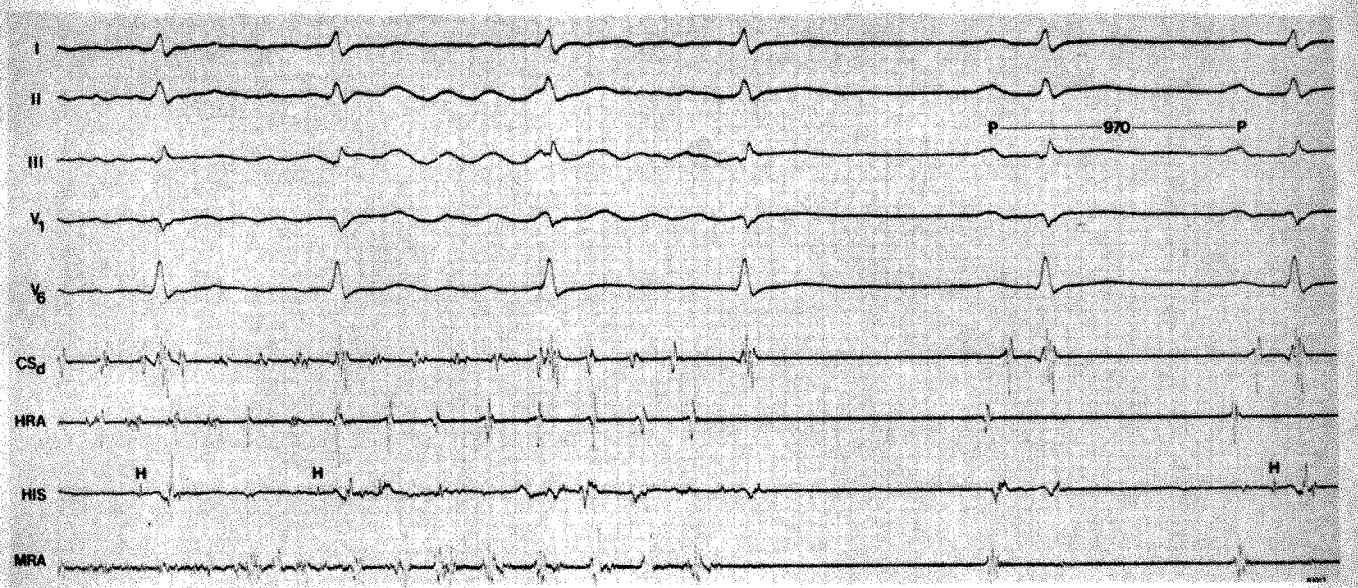

FIGURE 4. Patient 1. Same organization of tracings as in Figures 2 and 3. A second burst of atrial pacing at a cycle length of 150 ms was applied (not shown) after the records shown in Figure 3. The records shown here followed this second burst of pacing. As before, pacing was followed by local fibrillation in the mid-right atrium (MRA) and His bundle region and overdrive acceleration of flutter in the high right atrium (HRA) and distal coronary sinus (CS_d). The surface electrocardiogram at this time showed atrial fibrillation (**left**). Organization of local fibrillation in the mid-right atrium and His bundle region then occurred, associated with slowing of the flutter rate in the high right atrium and coronary sinus and a reappearance of flutter waves in the surface electrocardiogram. This was quickly followed by a return to sinus rhythm (**right**).

pacing at a cycle length of 150 ms was applied. Immediately after this second period of pacing, the overdrive acceleration was still present (Fig. 4). However, local fibrillation in the mid and low right atrium gradually organized into discrete electrograms, concomitant with slowing of the flutter rate at other sites and a reappearance of flutter waves in the surface electrocardiogram. This was followed by an abrupt return to sinus rhythm (Fig. 4). Atrial flutter could not be reinitiated by either single or multiple atrial premature depolarizations, regardless of their degree of prematurity or site of origin.

Patient 2

Atrial recordings during flutter (Fig. 5): Although sinus rhythm was present at the beginning of the study, sustained atrial flutter was provoked by a spontaneously occurring atrial premature depolarization. The atrial flutter was characterized by a rate of 340/min (cycle length 175 ms between successive atrial waves recorded in the coronary sinus), and a 2:1 A-V relationship and flutter waves in the surface electrocardiogram that were predominantly negative in the inferior leads. The atrial activation sequence during flutter revealed earliest activity appearing nearly simultaneously in the coronary sinus and low right atrium in the region of the His bundle, followed by later activation of the high right atrium. At the former two recording sites the interval between successive atrial waves was 175 ms and quite constant. In contrast, atrial electrograms recorded from the high right atrium demonstrated a regularly irregular, repeating pattern. Careful inspection revealed that this was due to progressive delay in conduction between the coronary sinus and the high right atrium, with conduction block of every third impulse at the latter site. The pattern of conduction between these 2 sites demonstrated Wenckebach periodicity.

Intravenous administration of 600 mg of procainamide resulted in a slowing of the atrial flutter rate to 285/min (cycle length 210 ms), as measured by successive atrial waves recorded in the coronary sinus. During procainamide infusion, conduction block between the coronary sinus and the high right atrium became variable, sometimes showing a 3:1 pattern and at other times a 4:3 or 5:4 Wenckebach periodicity. Thirty minutes after completing the drug infusion the rhythm spontaneously reverted to sinus rhythm.

Discussion

Mechanisms of atrial flutter: Controversy regarding the mechanism of atrial flutter in human beings has centered around 2 divergent views. One of these holds that the arrhythmia is due to circus movement which incorporates most or all of the atrial myocardium as the reentrant pathway.[1,2] Other investigators[3–5] have felt that a focal origin, whether the result of reentry, enhanced automaticity or triggered activity, is more likely. Experimental studies[7–9] in isolated rabbit atrial muscle suggest that, although circus movement may well be the underlying mechanism, the reentrant pathway is in fact as small as physiologically possible, determined predominantly by the constraints of atrial refractoriness. Because the reentrant circuit is so small in this model, atrial flutter arising by such a mechanism can be thought of as basically focal in origin. Many clinical studies[10–12] utilizing programmed electrical stimulation of the heart tend to support this view.

Focal origin of atrial flutter with interatrial conduction delay: Both patients in the present study demonstrated interatrial dissociation or conduction delay phenomena during spontaneous atrial flutter which suggested that a significant portion of the right atrium was not essential for maintenance of the arrhythmia. This observation, therefore, supports the notion of a focal origin of atrial flutter. In Patient 2, for example, multiple intracavitary recordings during flutter revealed a 3:2 relation between depolarization in the left atrium (coronary sinus) and in the high right

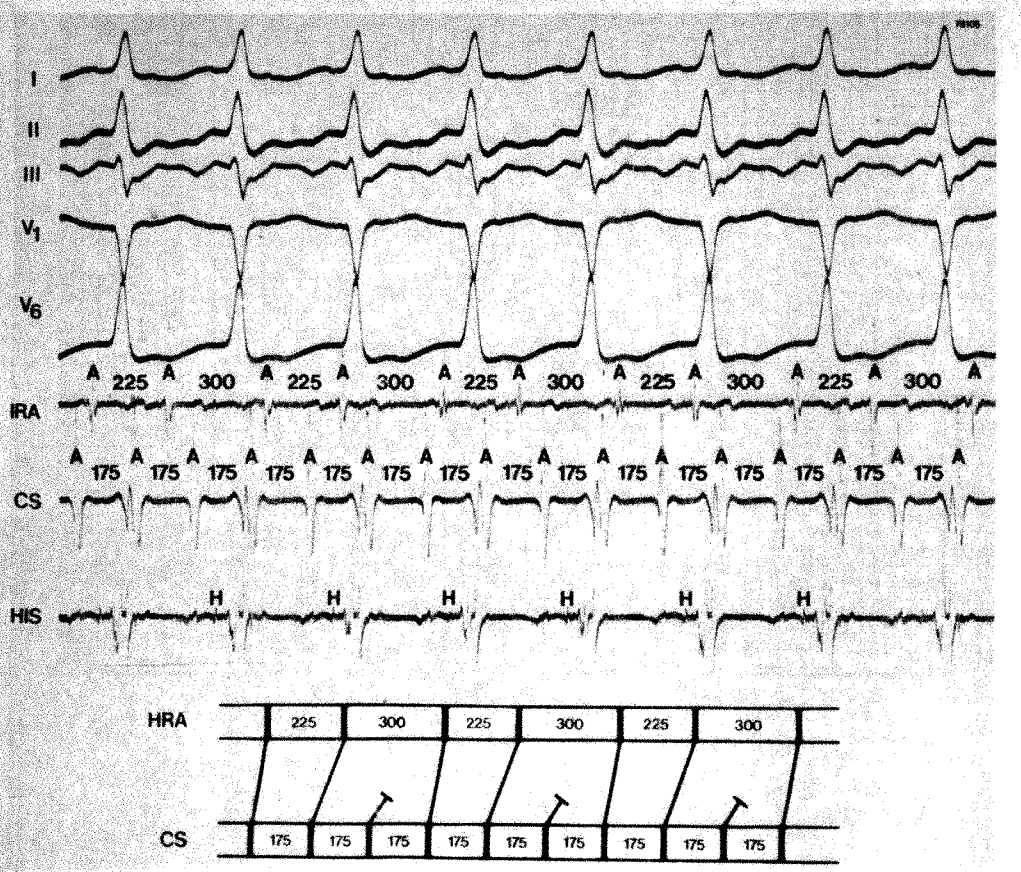

FIGURE 5. Patient 2. **Top panel,** simultaneous recording of **(top to bottom)** electrocardiographic leads I, II, III, V_1, and V_6, as well as electrograms from the high right atrium (HRA), coronary sinus (CS), and His bundle region during spontaneous atrial flutter. The cycle length of atrial depolarization in the coronary sinus is 175 ms and constant throughout, whereas atrial electrograms in the high right atrium occur with a regularly irregular, repeating pattern. The pattern of atrial depolarization in the His bundle region is probably the same as in the coronary sinus, although this is somewhat obscured by the proximity of these electrograms to the local ventricular electrogram. **Bottom panel,** Lewis diagram of atrial depolarization in the coronary sinus (CS) and high right atrium (HRA) during atrial flutter as shown in the **top panel.** 3:2 Wenckebach conduction between the coronary sinus and high right atrium could account for the observed patterns of recorded atrial electrograms.

atrium, the time relations being consistent with 3:2 Wenckebach conduction between the 2 regions. Electrographic atrial deflections recorded from the coronary sinus occurred at a constant rate of 340/min, identical to the rate of the flutter waves in the surface electrocardiogram. Furthermore, the coronary sinus was 1 of the earliest regions activated during flutter. These observations suggest that left atrial tissue in the coronary sinus was an integral part of the focus causing flutter, whereas activation of the high right atrium represented merely passive, variable conduction from the flutter focus. Similar interatrial conduction delay has been reported for paroxysmal atrial tachycardia originating in a left atrial focus.[13,14] Interatrial conduction delay and block have also been reported during atrial flutter in a patient with preexcitation,[15] but this was after intravenous administration of propranolol and it occurred transiently immediately before resumption of sinus rhythm. Sustained interatrial conduction delay during sustained flutter in the absence of drug effect has not been described previously.

Persistent local atrial fibrillation with persistent flutter at other sites: Observations in Patient 1 during spontaneous atrial flutter also suggested a focal origin of the arrhythmia. In this patient rapid atrial pacing at a cycle length of 150 ms resulted in local fibrillation in the mid right atrium and low right atrial septum (His bundle region) which persisted after termination of pacing, whereas recordings from the high right atrium and coronary sinus continued to show discrete, repetitive electrograms typical of flutter (Fig. 3). Since atrial flutter persisted in the high right atrium and coronary sinus even though other areas of the right atrium were fibrillating, clearly these other areas were not essential for maintenance of the flutter. Persistent local fibrillation at some sites with persistent flutter at others is rare.[14,16] One recent report[16] described a patient in whom localized sinus rhythmn was present in the high right atrium, atrial fibrillation in the left atrium, and areas of rapid, regular flutter-like activity at other sites in the right atrium. However, the predominant rhythm in the patient was probably atrial fibrillation in view of the ineffectiveness of both rapid atrial pacing and DC cardioversion to restore sinus rhythm. In our Patient 1 one also might argue that the rhythm present after pacing at a cycle length of 150 ms was, in fact, atrial fibrillation, with only apparent rather than true flutter in the high right atrium and coronary sinus. However, this was demonstrated not to be the case by a second burst of rapid atrial pacing which resulted in a return to sinus rhythm. Reversion to sinus rhythm after rapid atrial pacing is typical of atrial flutter but not atrial fibrillation.

Clinical and therapeutic implications: From a clinical standpoint our observations in Patient 1 are of particular importance since they underscore the limitations of the surface electrocardiogram in defining atrial rhythm. After the first burst of rapid atrial pacing

at a cycle length of 150 ms, this patient's electrocardiogram revealed atrial fibrillation or, at best, flutter-fibrillation, without discrete, regularly repeating flutter waves (Fig. 3). Such rhythms have been thought to be unresponsive to rapid atrial pacing.[14,17] In spite of the electrocardiographic appearance of atrial fibrillation in this patient and the documented presence of local atrial fibrillation at some sites in the right atrium, the predominant rhythm was atrial flutter which could be terminated by rapid atrial pacing. It may be that other patients with so-called flutter-fibrillation or impure flutter who were previously assumed to require pharmacologic intervention or DC cardioversion may, instead, be effectively treated with rapid atrial pacing, thus sparing them the risks inherent in these other therapies. One should not discard rapid atrial pacing as ineffective in any given patient unless multiple pacing rates and multiple pacing sites have been thoroughly explored.

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Echocardiographic Features of Carcinoid Heart Disease

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We reviewed the records of the Mayo Clinic patients with known carcinoid syndrome in whom echocardiographic studies had been done. Nineteen patients had M-mode and 2-dimensional echocardiographic examinations, and 1 patient had an M-mode examination only. Of the 20 patients, 8 had no evidence by echocardiogram of carcinoid heart disease; 2 had changes in the tricuspid valve echogram suggestive of early carcinoid heart disease, and the other 10 patients had the following distinctive echocardiographic findings: (1) the pattern of right ventricular volume overload (enlarged right ventricle with abnormal septal motion); (2) abnormal right-sided valves, including (a) a striking appearance of the tricuspid valve, the leaflets appearing thickened, retracted, and fixed in a semiopen position throughout the cardiac cycle, and (b) thickened, retracted pulmonic valve cusps, when visualized; and (3) the left-sided valves and chambers rarely involved. These echocardiographic features are distinctive of advanced carcinoid heart disease and correlate closely with pathologic findings.

Nearly 50 years ago, a distinct form of heart disease was described in patients with carcinoid syndrome.[1–3] It has since been recognized that cardiac involvement occurs as a late complication in approximately half of patients with carcinoid syndrome.[4,5] In many, the predominant terminal symptoms and death may be attributed directly to cardiac involvement.[4,6,7] Cardiac pathologic findings in carcinoid heart disease are characterized by peculiar endocardial lesions[4,8] that are specific for the disease and that may lead to significant hemodynamic derangements. They most often involve the pulmonic and tricuspid valves.

The clinical, electrocardiographic, radiologic, hemodynamic, and pathologic features of carcinoid heart disease have been well described.[4,5,7–12] A case report describing echocardiographic features of carcinoid heart disease was recently published.[13] This report describes distinctive echocardiographic features of carcinoid heart disease and correlates these findings with clinical and pathologic features of this disease.

Methods

Patients: The study group of 20 patients included all patients with carcinoid syndrome evaluated at the Mayo Clinic between 1977 and April 1982 for whom echocardiographic data of good quality were available (combined M-mode and 2-dimensional (2-D) examinations in 19 patients with M-mode only in 1 patient). All 20 patients had a diagnosis of malignant carcinoid disease proved by biopsy and were sent for echocardiographic examination. Five were sent for baseline examinations, and the M-mode and 2-dimensional examinations were normal. Fifteen patients were believed to have some evidence of carcinoid heart disease after clinical evaluation. Ten had the distinctive echocardiographic findings of carcinoid heart disease (Group I). The remaining 5 had either normal echocardiograms or evidence of some other heart disease (mitral valve prolapse, ischemic heart disease). These 5 patients and the 5 sent for baseline examinations constituted the other study group (Group II).

M-mode echocardiography: M-mode echocardiograms were obtained with a commercially available ultrasonoscope (Smith Kline Instruments, Ekoline 20A, or Irex System II) and were recorded with a multichannel strip-chart recorder (Cambridge, Honeywell 1856, or Irex). Studies were performed with a 2.25 MHz transducer with a repetition rate of 1,000 Hz.

The end-diastolic measurements for cavity size were taken at the peak of the R wave of the electrocardiogram. Systolic measurements of left ventricular internal dimensions were done at the peak of posterior wall motion. An estimate of global left ventricular function was determined by fractional shortening: $[(D_d - D_s)/D_d] \times 100$, where D_d and D_s are left ventricular dimensions at end-diastole and end-systole, respectively.

2-D echocardiography: 2-D echocardiographic examinations were performed with a commercially available wide-angle, phased-array sector scanner (Varian Associates, model V-3000 or V-3400). The transducers, with a frequency of 2.25 MHz, had 32 piezoelectric crystals in linear array. Images were recorded directly on a ¾ inch videocassette recorder (Sony VO-2800). Patients were examined supine or in a left semilateral decubitus position. The cross-sectional views of the heart were obtained from the parasternal, apical, and subcostal positions.[14] By qualitative analysis, left ventricular size and function, right atrial, right ventricular, and left atrial size, ventricular septal motion, and valvular structure were designated normal or abnormal. Abnormalities were graded as mild, moderate, or severe.

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Results

Clinical Findings

Group I, 10 patients (Table I): There were 7 women and 3 men, aged 20 to 72 years (mean 52). The site of origin of the primary carcinoid lesion, determined in 4 patients, was the colon in 2 and the ileum in 2. Hepatic metastases were present in 9 patients. Peak quantities of 5-hydroxyindoleacetic acid in 24 hour urine samples were abnormally high in 3 patients. They were normal in 1 patient, who had abnormally high serum levels of serotonin. In 1 patient the determination was not made. On the basis of cardiovascular examination, tricuspid valve disease with regurgitation or combined stenosis and regurgitation was suspected in all 10 patients. Jugular venous pressure was elevated in all 10 patients. Diastolic decrescendo murmur, probably representing aortic valve regurgitation, was noted in 1 patient. Nine patients were in New York Heart Association[15] class III or IV at the time of the echocardiographic examination, and 1 patient was in class I.

The electrocardiograms of all 10 patients showed sinus rhythm. One patient had first degree atrioventricular block, and 1 patient had complete right bundle branch block and prolonged Q-T interval. Other electrocardiographic abnormalities were atrial conduction delay (1 patient), right-axis deviation (1), right atrial enlargement (1), right ventricular hypertrophy (1), nonspecific S-T and T-wave abnormalities (4), and low anterior forces (1).

Chest roentgenograms were normal in 3 patients, cardiomegaly was present in 5, and pleural effusion was present in 4.

Six patients died between the time of the echocardiographic examination and completion of this study. Four patients were still living at the time of this study, 7 months to 10 years after the clinical diagnosis of carcinoid syndrome had been made.

Group II, 10 patients (Table I): Seven female and 3 male patients were included. The ages ranged from 40 to 76 years (mean 60). The site of origin of the primary lesion, determined in 8 of the 10 patients, was the ileum in 7 and the colon in 1. Hepatic metastases were present in all 10 patients. Urinary levels of 5-hydroxyindoleacetic acid were elevated in 9 patients and normal in 1. In 3 patients no murmurs were noted. Basal flow murmurs were noted in 2 patients, an apical systolic murmur and mid-systolic click suggestive of mitral regurgitation were noted in 1 patient, a grade 3 systolic murmur suggestive of tricuspid insufficiency was noted in 1, and murmurs suggestive of combined mitral and aortic regurgitation were noted in 1. Jugular venous pressure was elevated in 4 patients and normal in the other 4.

The electrocardiograms of all 10 patients showed sinus rhythm. In 5 patients the findings were normal. Two patients had nonspecific ST-T wave abnormalities. One patient had first degree atrioventricular block and complete left bundle branch block, and 1 had sinus tachycardia and right-axis deviation.

Chest roentgenographic findings were normal in 8 patients; 1 patient had pulmonary congestion and 1 had a pleural effusion, but heart size was normal in both.

Three patients died between the time of echocardiographic examination and completion of this study. Seven patients were still alive at the time of this study,

TABLE I Clinicopathologic Findings in 10 Patients (Cases 1 to 10) With Carcinoid Heart Disease and 10 Patients (Cases 11 to 20) Without Demonstrated Cardiac Involvement

Case	Age (yr) & Sex	Site of Primary Lesion	LM	Murmur	Peak 5-HIAA	ECG	CE by X-ray	PE by X-ray	NYHA Class	Time (mo) From Diagnosis Until Death
1	58F	Unknown	+	Gr 3/6 SEM	493	Normal	+	+	III	8
2	72F	Unknown	+	Gr 3/6 SEM	280	RBBB	+	+	III	4
3	66F	Colon	+	Gr 3/6 syst, 1/6 diast	240	1° AVB	0	0	III	48
4	62F	Colon	+	Gr 3/6 syst	220	NSST-T	+	0	III	144
5	52F	Ileum	+	Gr 2/6 syst, 2/6 diast	213	RAD; NSST-T	+	+	III	48
6	53M	Unknown	+	Gr 3/6 diast	1,020	NSST-T	+	0	III	Alive (60)
7	20F	Ileum	Scan ± normal	Gr 2/6 syst, 2/6 diast	70	RVH	0	0	I	Alive (7)
8	36M	Unknown	+	Gr 4/6 syst, S_3	...	ST	0	+	IV	2 weeks
9	58M	Unknown	+	Gr 2/6 syst, S_3	515	Normal	0	+	III	Alive (120)
10	42F	Unknown	+	Gr 3/6 diast, 4/6 syst	340	ST	0	0	III	Alive (16)
11	71F	Unknown	+	Gr 2/6 SEM	252	Minor LAD	0	0	...	Alive (1)
12	71F	Ileum	+	0	211	WNL	0	0	...	Alive (66)
13	56M	Ileum	+	Gr 2/6 holosystolic	268	NSST-T	0	0	...	60
14	61F	Colon	+	0	260	NSST-T	0	+	...	18
15	64F	Ileum	+	Gr 2/6 SEM	79	Normal	0	0	...	108
16	76F	Ileum	+	Gr 3/6 holosystolic	3	1° AVB; LBBB	0	0	...	Alive (2) weeks
17	62F	Ileum	+	Gr 1/6 SEM	297	Normal	0	0	...	Alive (36)
18	53M	Ileum	+	Gr 2 syst	288	ST	0	0	...	Alive (30)
19	40M	Ileum	+	0	445	ST; RAD	0	0	...	Alive (14)
20	48F	Unknown	+	Gr 3 syst	145	Normal	0	0	...	Alive (12)

CE = cardiac enlargement; diast = diastolic; ECG = electrocardiogram; 1° AVB = first-degree atrioventricular block; 5-HIAA = 5-hydroxyindoleacetic acid (normal, <6 mg/24 h); Gr = grade; LAD = left axis deviation; LBBB = left bundle branch block; LM = liver metastasis; NSST-T = nonspecific abnormality of the S-T segments and T waves; NYHA = New York Heart Association; PE = pleural effusion; RAD = right-axis deviation; RBBB = right bundle branch block; RVH = right ventricular hypertrophy; SEM = systolic ejection murmur; ST = sinus tachycardia; syst = systolic; WNL = within normal limits; + = yes; 0 = no.

TABLE II M-Mode Echocardiographic Findings in Patients With Carcinoid Heart Disease

Case	Mitral Leaflets	Aortic Valve Cusps	LA Size (mm)	Tricuspid Leaflets	VS Thickness (mm) in Diastole	LV Posterior Wall Thickness (mm) in Diastole	$LVID_d$ (mm)	$LVID_s$ (mm)	FS (%)	$RVID_d$ (mm)	Pericardial Effusion
1	Prolapse	Normal	30	Thickened; ↓ excursion	9	9	42	28	33	30	0
2	Normal	Normal	33	Poorly visualized	9	9	36	25	31	46	0
3	Normal	Normal	34	↓ excursion	11	9	40	16	40	30	+
4	Normal	Normal	27	Poorly visualized	8	8	46	24	47	28	+
5	Diastolic flutter	Normal	36	Thickened; ↓ excursion	9	9	41	...	...	33	0
6	Interrupted A-C interval	Normal	38	Thickened; ↓ excursion	10	10	50	34	32	41	0
7	Diastolic flutter	Normal	22	Thickened	6	7	40	20	50	42	0
8	Normal	...	32	Poorly visualized	8	8	48	30	38	35	+
9	Normal	...	25	Thickened; ↓ movement	7	9	44	30	32	...	0
10	Normal	Normal	29	Thickened; ↓ motion	10	7	37	28	30	34	0
14*	Thickened	Multiple echoes	38	Thickened	11	9	47	27	43	19	++
15*	Normal	Thickened	30	Thickened	...	8	...	...	...	...	0
17*†	Normal	Normal	39	Thickened	12	10	40	24	40	29	+

* See text. † Second examination, 1982.
FS = fractional shortening; LA = left atrium; LV = left ventricle; $LVID_d$ = left ventricular inner dimension in diastole; $LVID_s$ = left ventricular inner dimension in systole; $RVID_d$ = right ventricular inner dimension in diastole; VS = ventricular septum; ↓ = diminished; 0 = no; + = small; ++ = moderate.

1 month to 5.5 years after the clinical diagnosis of carcinoid syndrome had been made.

Echocardiographic Findings

Group I, M-mode echocardiographic findings (Table II): All 10 of the patients with carcinoid heart disease had the features of right ventricular volume overload (enlarged right ventricle and abnormal motion of the ventricular septum). In 6 of the 10 patients, the tricuspid valve was greatly thickened and had either greatly diminished excursion or an undulating motion during the cardiac cycle. The tricuspid valve echo could not be recorded in 3 patients. Diastolic fluttering of the anterior leaflet of the tricuspid valve was noted in 1 patient. The pulmonic valve echogram was not recorded in any of the 10 patients.

The left ventricular wall thickness, left ventricular cavity, and left atrial size were normal in all patients. The mitral valve appeared normal in 9 patients. (The patient with aortic regurgitation and 1 additional patient had diastolic fluttering of the anterior mitral valve leaflet.) One patient (1) had mitral valve prolapse. Small (posterior) pericardial effusions were present in 3 patients.

2-D echocardiographic findings (Table III): Of the 9 patients with carcinoid heart disease who had 2-D echocardiographic examination, all had right ventricular volume overload (Fig. 1), which confirmed the M-mode findings. The most striking abnormalities were found when the tricuspid valve was examined. The leaflets, specifically anterior and septal, were thickened and retracted and had greatly diminished mobility (4 had essentially no mobility, and 3 had slight motion at the extreme tip of the anterior tricuspid leaflet) (Fig. 2). There was incomplete coaptation of the anterior and the septal leaflets. The leaflets appeared fixed in a semiopen position, so that the orifice remained open throughout the cardiac cycle (Fig. 3 and 4). In 1 patient with severe heart disease, mobility was retained in the anterior tricuspid leaflet, but the septal leaflet was rigid and normal coaptation failed. In 2 patients, adequate visualization of the subvalvular structures demonstrated

TABLE III Two-Dimensional Echocardiographic Findings in Patients With Carcinoid Heart Disease*

Case	Mitral Valve	Aortic Valve Cusps	Tricuspid Leaflets	Pulmonic Cusps	PE	AS
1	Prolapse	Normal	Thickened, retracted	Poorly visualized	+	Bulges left
2	Normal	Thickened	Thickened, retracted, fixed	Thickened, retracted	0	Inadequately visualized
3	Normal	Normal	Thickened; ↓ mobility	Thickened	0	...
4	Normal	Thickened	↓ mobility	Poorly visualized	0	Bulges left
5	Normal	Normal	Thickened, fixed	Thickened; ↓ motion	0	Bulges left
6	Mild systolic bowing, posterior; diastolic fluttering, anterior	Normal	Thickened, retracted	Poorly visualized	0	...
8	Normal	Normal	Septal thickened	Not seen	+	Bulges right
9	Normal	Normal	Thickened, retracted, fixed	Thickened; retracted	0	Normal
10	Normal	Normal	Septal thickened, immobile	Retracted	0	Normal

* A 2-D examination was not done in Patient 7.
AS = atrial septum; LA = left atrium; PE = pericardial effusion; ↓ = diminished; 0 = none; + = small.

thickening and shortening of the chordae tendineae and papillary muscles. The pulmonary valve cusps, recorded in only 4 patients, were also shortened, thickened, and immobile. These difficulties were encountered in spite of diligent efforts to develop the pulmonary valve echogram and good visualization of right ventricular outflow. The findings were clearly recognized as abnormal by all observers.

The structure and motion pattern of the mitral valve appeared normal in 7 of the 9 patients. The patient in whom mitral valve prolapse was demonstrated by M-mode echocardiogram had prolapse of the posterior leaflet by 2-D examination. The size and function of the left ventricle appeared normal in all patients.

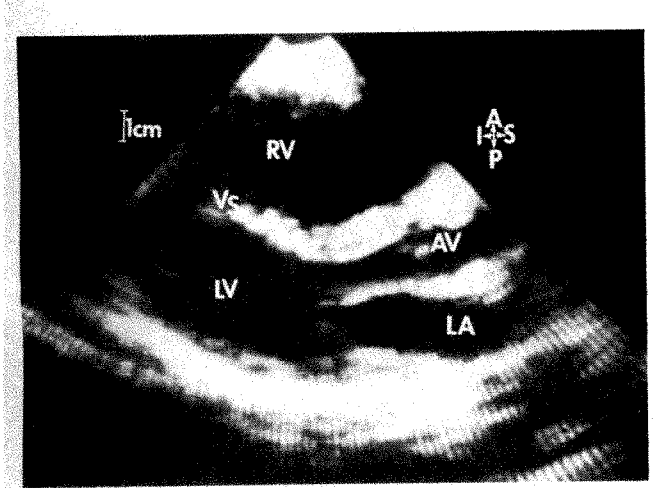


FIGURE 1. Patient 5. Long-axis view of the left ventricle (diastolic frame) shows a normal left ventricle (LV) and left atrial (LA) size, and normal mitral and aortic (AV) valves. The right ventricle (RV) is moderately dilated, and the basal ventricular septum (VS) has an abnormal bulge toward the left ventricle during diastole (abnormal septal motion). A = anterior; I = inferior; P = posterior; S = superior.

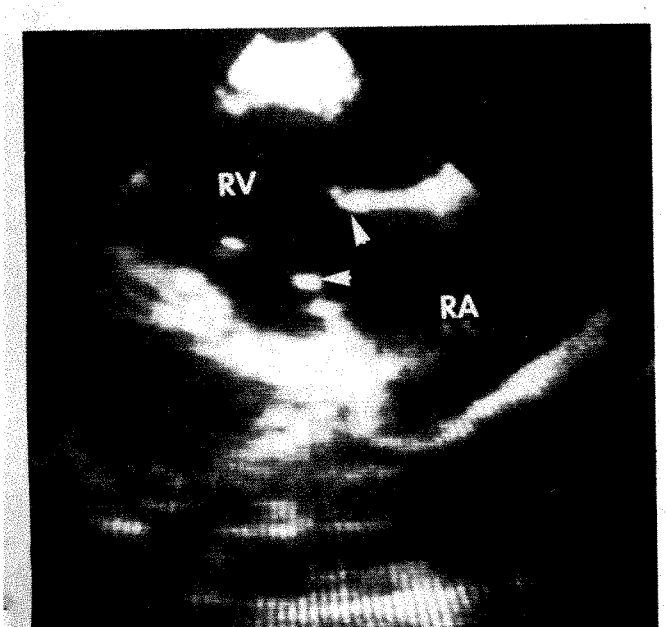


FIGURE 2. Patient 5. Long-axis view of right ventricular inflow shows an enlarged right ventricle (RV) and right atrium (RA). Thickened and retracted anterior and septal leaflets (**arrows**) of the tricuspid valve exhibited little motion during real-time examination and resulted in a fixed orifice.

Group II, M-mode echocardiographic findings: The M-mode echocardiograms were normal in 8 of the 10 patients without demonstrated carcinoid heart disease. One patient had thickening and diminished excursion of the anterior tricuspid valve leaflet but no evidence of right ventricular volume overload. When the M-mode echocardiograms were reexamined, 2 patients (Table II) had changes in the tricuspid valve echogram suggestive of early carcinoid heart disease. One patient had a hyperdynamic heart.

One patient (17) was reexamined 3 years after the initial, normal echocardiogram (Table II). At the time of the second examination (1982), the right ventricle was enlarged and septal motion was abnormal. The septal leaflet of the tricuspid valve was thickened, and mobility was reduced. The anterior tricuspid leaflet appeared normal. The pulmonary valve appeared thickened. The left-sided valves and chambers were normal.

2-D echocardiographic findings: Of the patients in Group II, 8 had essentially normal 2-D echocardiograms. There were instances of calcification in the mitral anulus and slight thickening of the mitral or aortic valve leaflets, findings not unusual in patients of this age. One patient had hyperdynamic cardiac activity but no structural changes in the valves or chambers. One patient had a pericardial effusion.

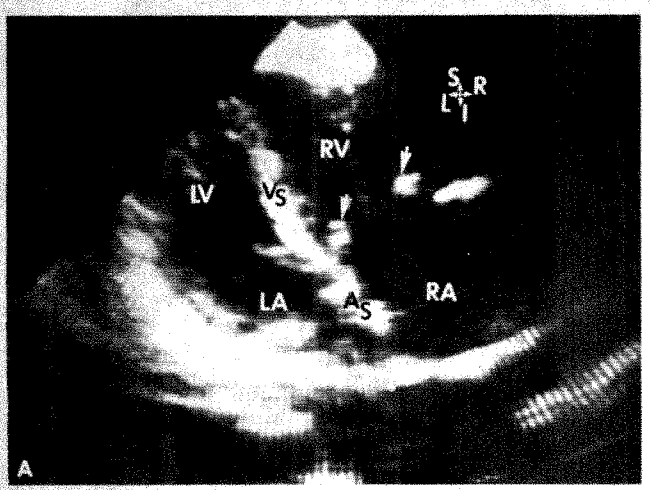
Discussion

Patients with malignant carcinoid tumors may live for many years after the first signs of this disease appear.[6] Some workers[16,17] have suggested that in patients with the slowly progressive form of the disease, cardiovascular lesions are more likely to develop because of the time involved. Cardiac involvement can cause severe and disabling symptoms when right ventricular failure supervenes. In many cases, the predominant terminal symptoms and death may be attributed to intractable right ventricular failure secondary to tricuspid and pulmonary valvular lesions.[18] Experience with successful surgical treatment of the valvular lesions in carcinoid heart disease is increasing, and a more aggressive surgical approach to the treatment of the cardiovascular complications of this disease has been proposed.[16–23] Therefore, accurate diagnosis and adequate treatment of the cardiac manifestations are imperative in the long-term management of patients with malignant carcinoid.

Definitive diagnosis of carcinoid heart disease may be difficult. Specific roentgenographic findings do not exist, although the right atrium or right ventricle may be enlarged.[4] Likewise, the electrocardiogram is of little specific help in diagnosis. Right bundle branch block, right-axis deviation, low QRS voltage, and prominent P waves suggesting right atrial enlargement have been noted in patients with carcinoid heart disease.[6] Similarly, the urinary levels of 5-hydroxyindoleacetic acid do not reflect the presence or absence of cardiac in-

volvement.[4] In addition, although the diagnosis of carcinoid heart disease usually is readily suspected by physical examination, some of the physical findings frequently encountered in the carcinoid syndrome—such as cyanosis, hepatomegaly, peripheral edema, ascites, and dyspnea—are not diagnostic of valvular disease in these patients. These signs may result from portal hypertension caused by hepatic obstruction from metastases.

The pathologic findings of carcinoid heart disease are distinctive.[4,9] Carcinoid plaques in the heart, histologically pathognomonic, represent mounds of endocardial (or intimal) smooth muscle proliferation. Although any cardiac chamber or great vessel may be involved, the



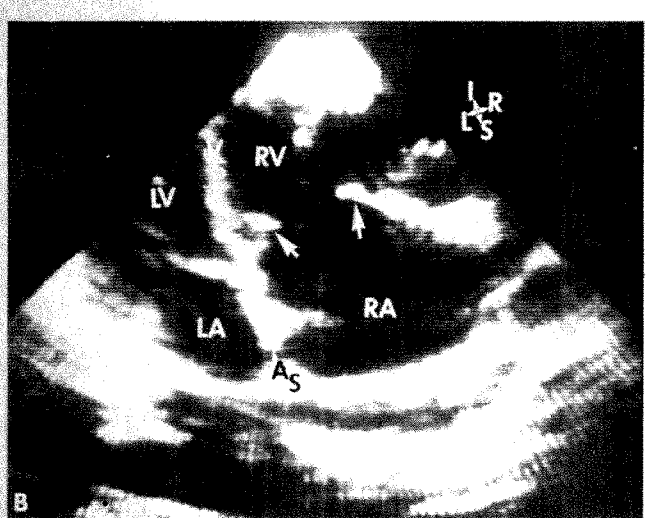


FIGURE 3. Patient 5. Four chamber view shows an enlarged right ventricle (RV) and right atrium (RA): **A,** diastolic frame; **B,** systolic frame. Note the typical appearance of the tricuspid valve as described in Figure 2 legend. Orifice is fixed in semiopen position and measures 2 cm across. AS = atrial septum; I = inferior; L = left; LA = left atrium; LV = left ventricle; R = right; S = superior; VS = ventricular septum.

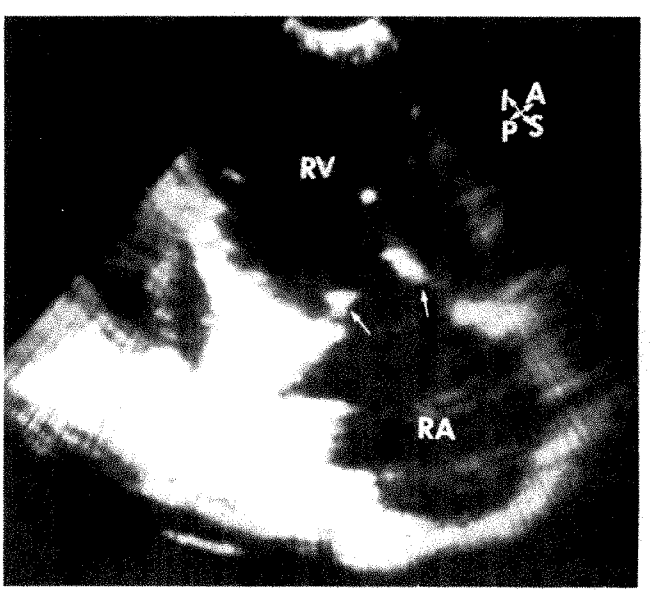


FIGURE 4. Patient 2. Right ventricular inflow view from the parasternal position shows an enlarged right atrium (RA) and right ventricle (RV). Note the thickened and retracted anterior and septal leaflets (**arrows**) of the tricuspid valve. This valve showed little movement during real-time examination (fixed orifice). A = anterior; I = inferior; P = posterior; S = superior.

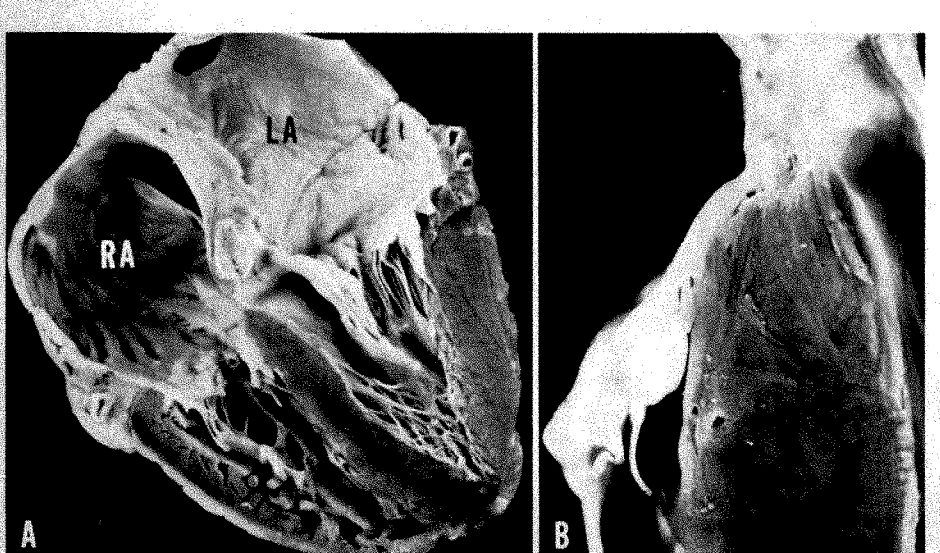


FIGURE 5. A, apical 4 chamber view of a cardiac specimen shows a normal left atrium (LA), mitral valve, and left ventricle and a dilated right atrium (RA), thickened tricuspid leaflets, and hypertrophied right ventricle. **B,** septal tricuspid leaflet thickened by carcinoid plaques and fused to underlying ventricular septum.

tricuspid and pulmonary valves are almost always the most severely involved.[4,8] All valvular components may be involved (anulus, leaflets, commissures, chordae tendineae, and papillary muscles). (Postmortem data in this series were not available for patients who died away from the medical center.)

In the tricuspid valve, circumferential anular involvement is common, and the resulting retraction produces a somewhat stenotic orifice of fixed size (Fig. 5). Plaques may obliterate the valvular commissures. Although such plaques may occur on the atrial or ventricular surfaces of the leaflets, ventricular involvement is more common (particularly of the septal and posterior leaflets), and adherence to the underlying endocardium may rigidly fix the thickened leaflets in semiopened position and result in significant regurgitation.[4] Plaques may also cause thickening and fusion of chordae tendineae and focal thickening of papillary muscles (Fig. 6 and 7).

Anular constriction of the pulmonary valve generally is pronounced and can result in hemodynamically significant stenosis.[4] The cusps are thickened and rigid but tend to be contracted and greatly reduced in size; thus, they contribute to valvular incompetence. Commissures may also be obliterated by plaques (Fig. 8).

This same 2-D appearance of the tricuspid valve in our patients with carcinoid heart disease was distinctive. The tricuspid valve leaflets were thickened and retracted, exhibiting diminished mobility and incomplete coaptation of anterior and septal leaflets. The leaflets remained in a semiopen position throughout the cardiac cycle.

The echocardiographic findings in 2 patients (14 and 15) are of interest. The right atrium and right ventricle

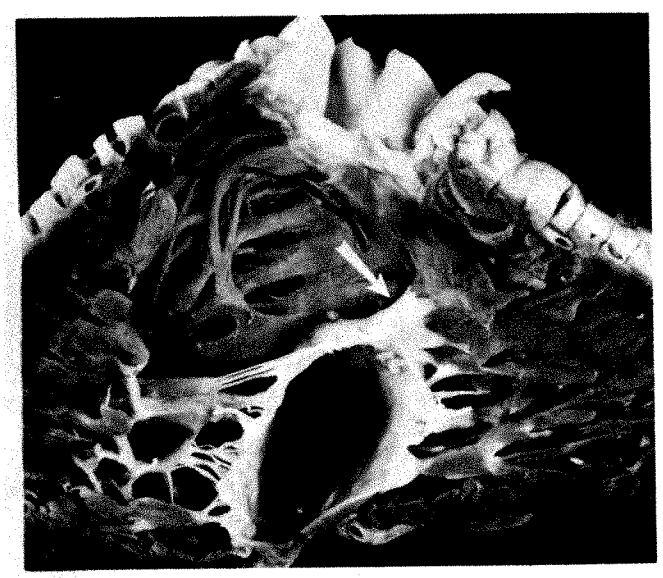


FIGURE 6. Opened right ventricle shows thickened leaflets, thickened and focally shortened and fused chordae tendineae, and extension of carcinoid plaque from the medial papillary muscle onto the inferior limb of the trabecula septomarginalis (**arrow**). The pulmonary valve is also thickened and retracted.

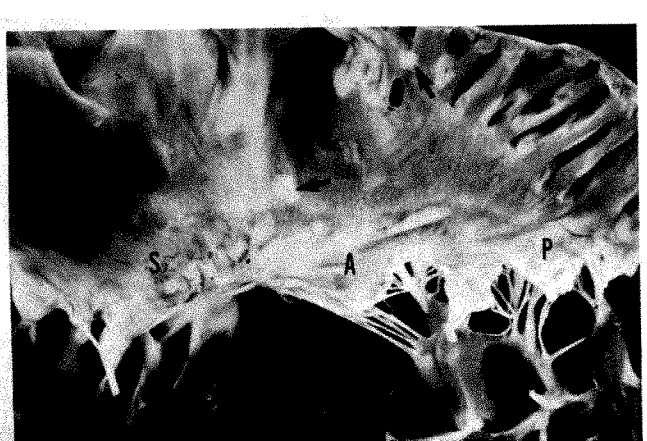


FIGURE 7. Opened tricuspid valve with thickened leaflets, vascularization of the anterior leaflet (A), obliteration of the commissure between the anterior and septal (S) leaflets, focal thickening of the chordae tendineae to the anterior and posterior (P) leaflets, encasement of the septal chordae tendineae by carcinoid plaques, and extension of the plaques onto the papillary muscles and right ventricular myocardium. Note the numerous right atrial endocardial carcinoid plaque (**arrows**).

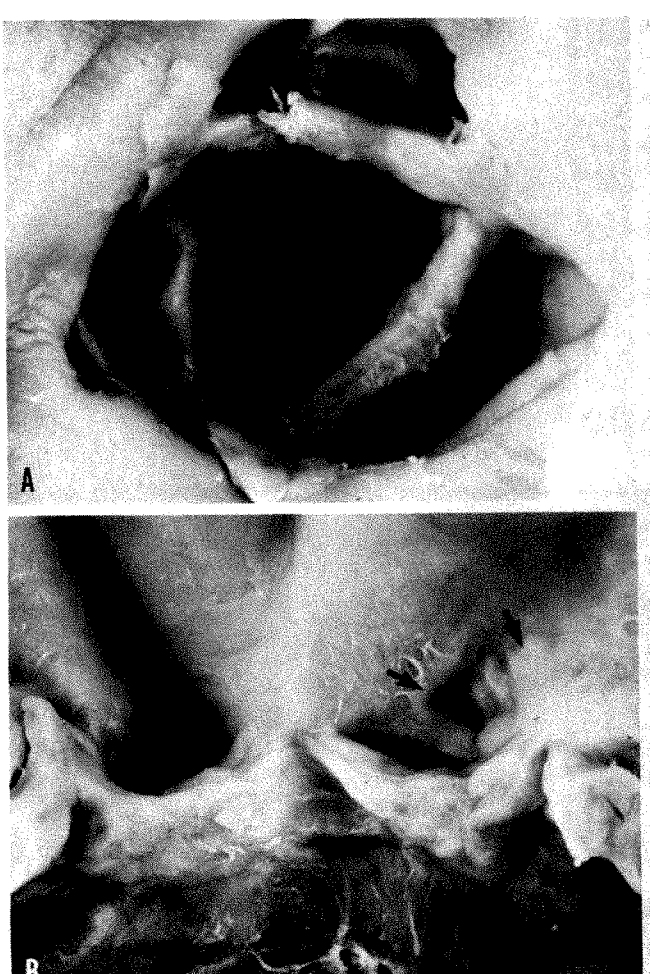


FIGURE 8. Pulmonary valve viewed from above (**A**) and opened (**B**). The thickened and retracted cusps result in valvular incompetence. The constricted anulus results in valvular stenosis. Carcinoid plaques (**arrows**) extend onto the pulmonary trunk.

were normal. In both patients, the anterior tricuspid leaflet was thickened but the excursion of the valve was normal. Although these findings are not specific, in patients who have malignant carcinoid syndrome they may represent early thickening of the tricuspid valve leaflets from carcinoid heart disease that has not yet caused demonstrable functional abnormalities. Unfortunately, postmortem examination was not done in either patient. Patient 17 was reexamined 3 years after a normal examination and was found to have thickening and loss of mobility of the septal leaflet of the tricuspid valve accompanied by early volume overload of the right ventricle. This case suggests that serial examinations may be important to demonstrate abnormalities more surely.

Our inability to image the pulmonary valve despite clear views of the right ventricular outflow tract and main pulmonary artery suggests that the pathologic process resulting in pulmonary valve contraction (greatly reduced cusp size) inhibited image formation (Fig. 8B). In patients with normal mitral and aortic valves, the findings of thickened, fixed, and retracted tricuspid valve leaflets and pulmonary cusp or cusps associated with an enlarged right ventricle and right atrium are virtually diagnostic of advanced carcinoid heart disease.

In the differential clinical diagnosis of tricuspid valvular disorders that may be associated with significant regurgitation, one must consider not only carcinoid heart disease but also rheumatic valvular disease, tricuspid valve prolapse, ruptured chordae tendineae, eosinophilic endomyocardial disease, endocardial fibroelastosis, Ebstein's anomaly, and congenital tricuspid dysplasia (dysgenesis). The echocardiographic features of these entities are specific and should allow differentiation. Rheumatic tricuspid valve involvement occurs almost always with rheumatic involvement of the left-sided valves, while the pulmonic valve is intrinsically normal and is usually readily visualized. Although left-sided valvular involvement by carcinoid heart disease has been reported,[10,12] the involvement of tricuspid and pulmonic valves just described is distinctive and should allow the correct diagnosis. The rheumatic tricuspid valve appears thickened and retracted and demonstrates a diastolic doming motion similar to that seen in mitral stenosis. Such doming motion was not seen in any case of carcinoid heart disease. Tricuspid insufficiency secondary to prolapse and ruptured chordae is characterized by increased tricuspid valve excursion associated with prolapse of leaflets into the right atrium. The 2-D features in Ebstein's anomaly are distinctive, consisting of downward displacement of the septal leaflet and elongation of the anterior leaflet. Eosinophilic endomyocardial disease and endocardial fibroelastosis may rarely involve the right side of the heart alone, but the tricuspid valve leaflets, in our limited experience, are normal or mildly thickened and have normal motion, and the pulmonary valve is normal. To date, in our experience, echocardiographic features similar to those in carcinoid tricuspid valve involvement have been seen only in 2 young patients (ages 10 and 14) with congenital tricuspid dysplasia. The pulmonic valve echogram was normal in both. The clinical history and the echocardiographic findings elsewhere in the heart should allow the differentiation of carcinoid heart disease from these other disorders.

In conclusion, the following 2-D echocardiographic findings appear specific for advanced carcinoid heart disease: (1) evidence of right ventricular volume overload; (2) abnormal right-sided valves, including (a) the distinct pattern of thickened, retracted tricuspid leaflets that fail to coapt in systole, and (b) thickened and retracted pulmonary valve cusps; and (3) absence of involvement of the left-sided valves and chambers. In addition, the early stages of tricuspid valve involvement appear to be thickening of the tricuspid leaflets, nearly normal motion, and normal cardiac chamber sizes. Considered in the context of cases with no or early cardiac involvement, these features should serve as a basis for early diagnosis and serial assessment of carcinoid heart disease.

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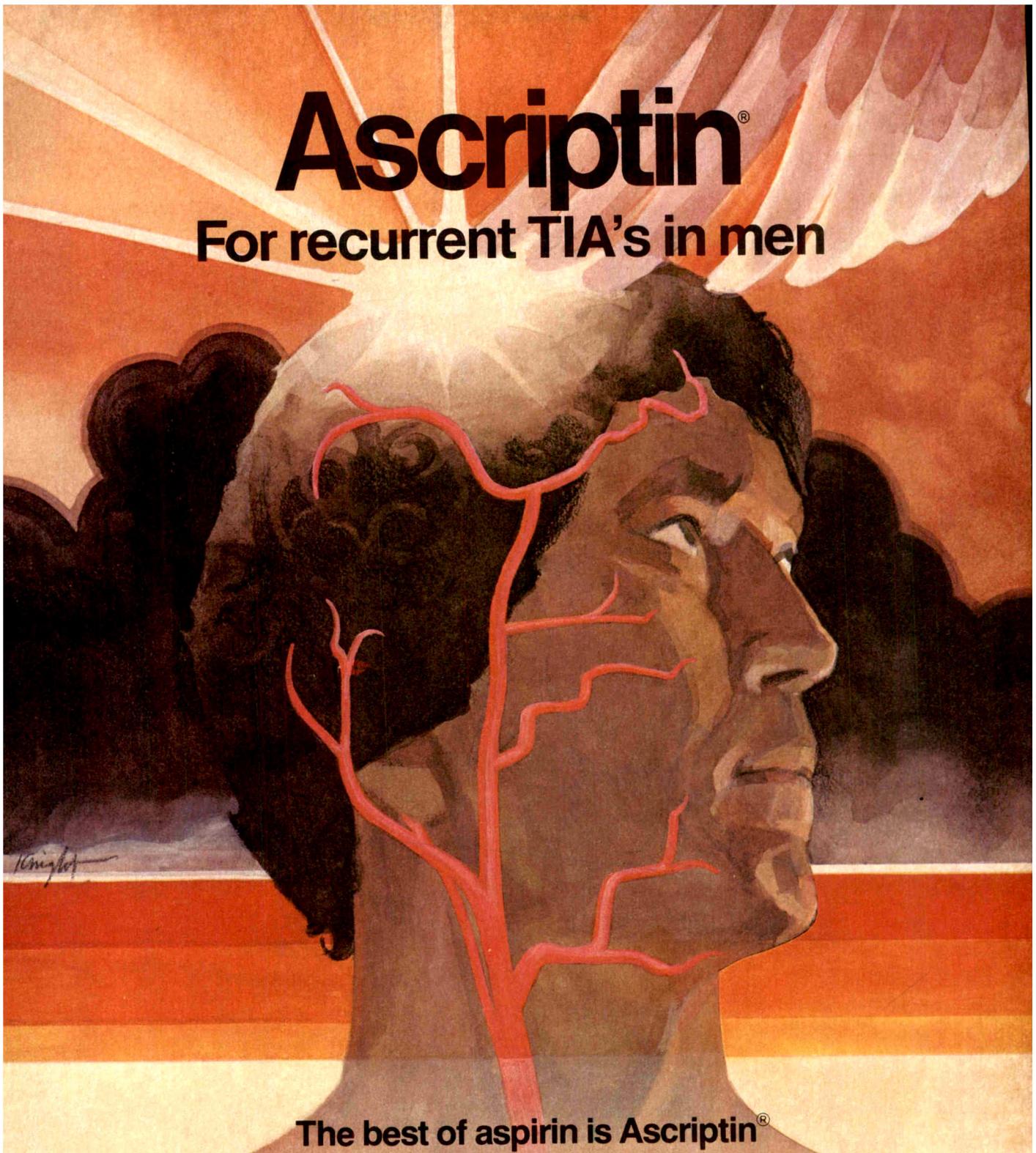

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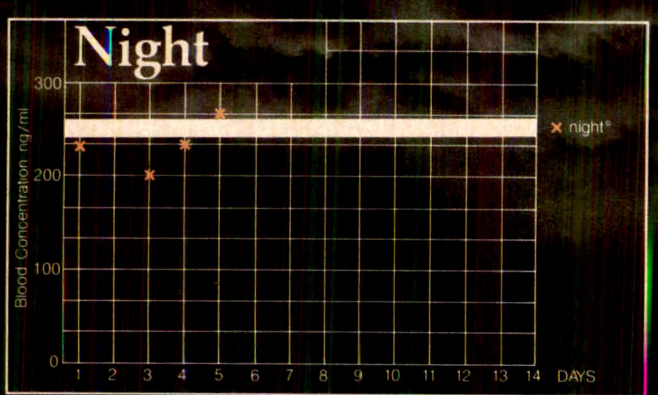

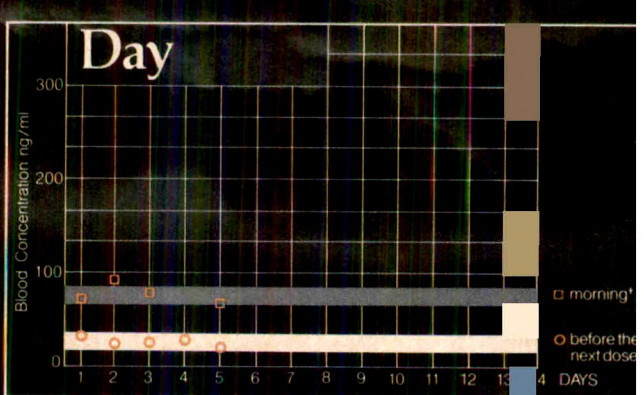

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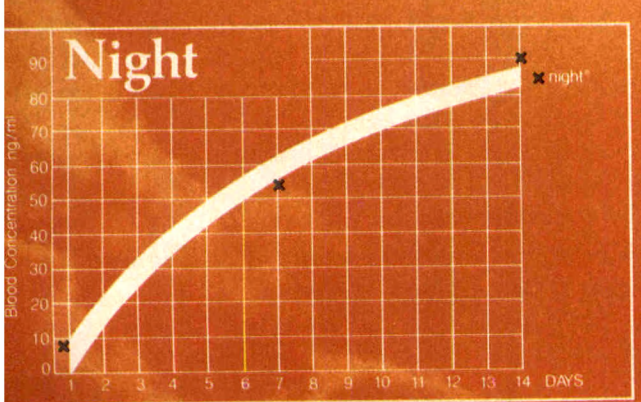

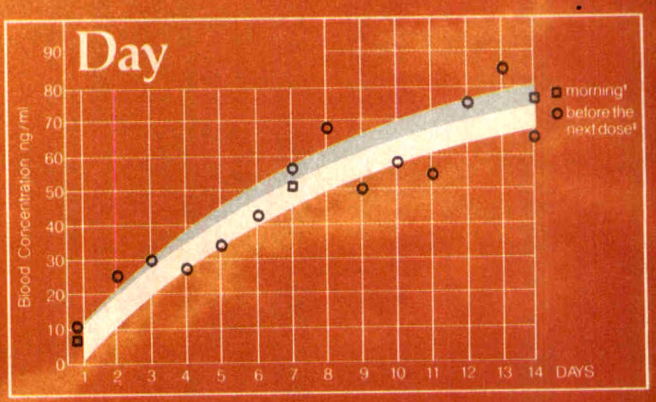

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1. Schwarz HJ: Br J Clin Pharmacol *8*:23s, 1979: Mean of 7 patients through 5 days of therapy projected to 14 days. Data on file indicate that steady-state values for plasma concentrations are reached by day 2 or 3.
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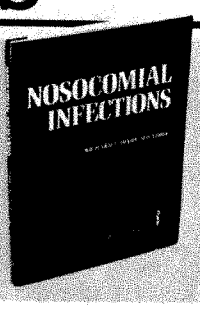

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CARDIOLOGY: 1982

The Second Issue of the New Annual providing a multidisciplinary approach to the latest, most important information on the state-of-the-art of cardiovascular medicine and surgery

written by:

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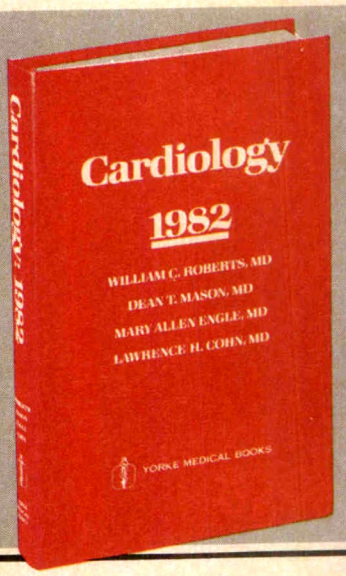

What is CARDIOLOGY 1982?

- The second in an annual series to be published in the SPRING each year
- A review of the year's newest and most important developments in cardiology — **665 papers**
- A multidisciplinary approach to clinical and applied research based on an exhaustive search of the year's literature
- A unique, cohesive summary of the state-of-the-art, written, not edited, by those making outstanding developments in the field
- A practical approach to a complicated and fast-moving subject designed to be read and used daily

CARDIOLOGY:1982 is NOT

- A collection of unrelated reviews
- An abstracting service
- A rehash of materials readily available elsewhere

CARDIOLOGY: 1982 provides in a concise and readable format and style fundamental and new information essential to understanding the current thinking on managing cardiovascular disease. It coordinates what's new with well-established data, arming the reader with a perspective on the field which is simply unavailable elsewhere. Its liberal use of illustrations and original tables condenses valuable information into instantly understandable knowledge.

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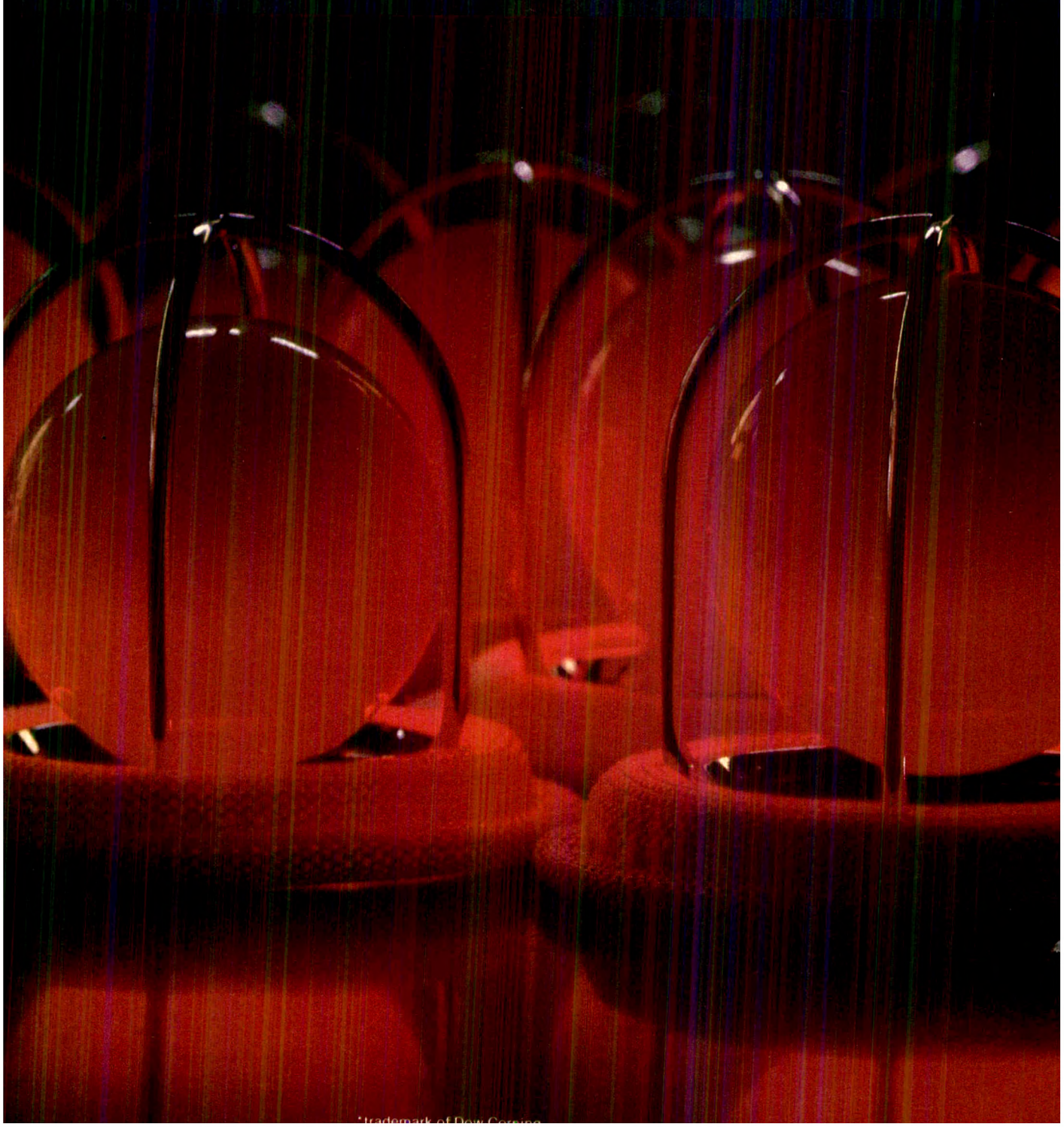

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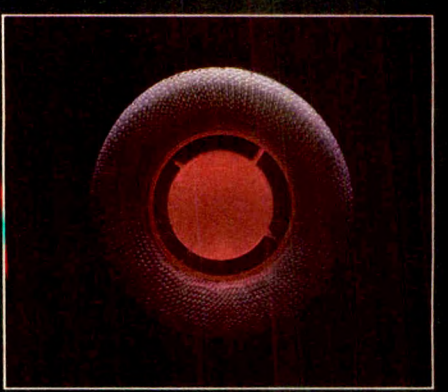

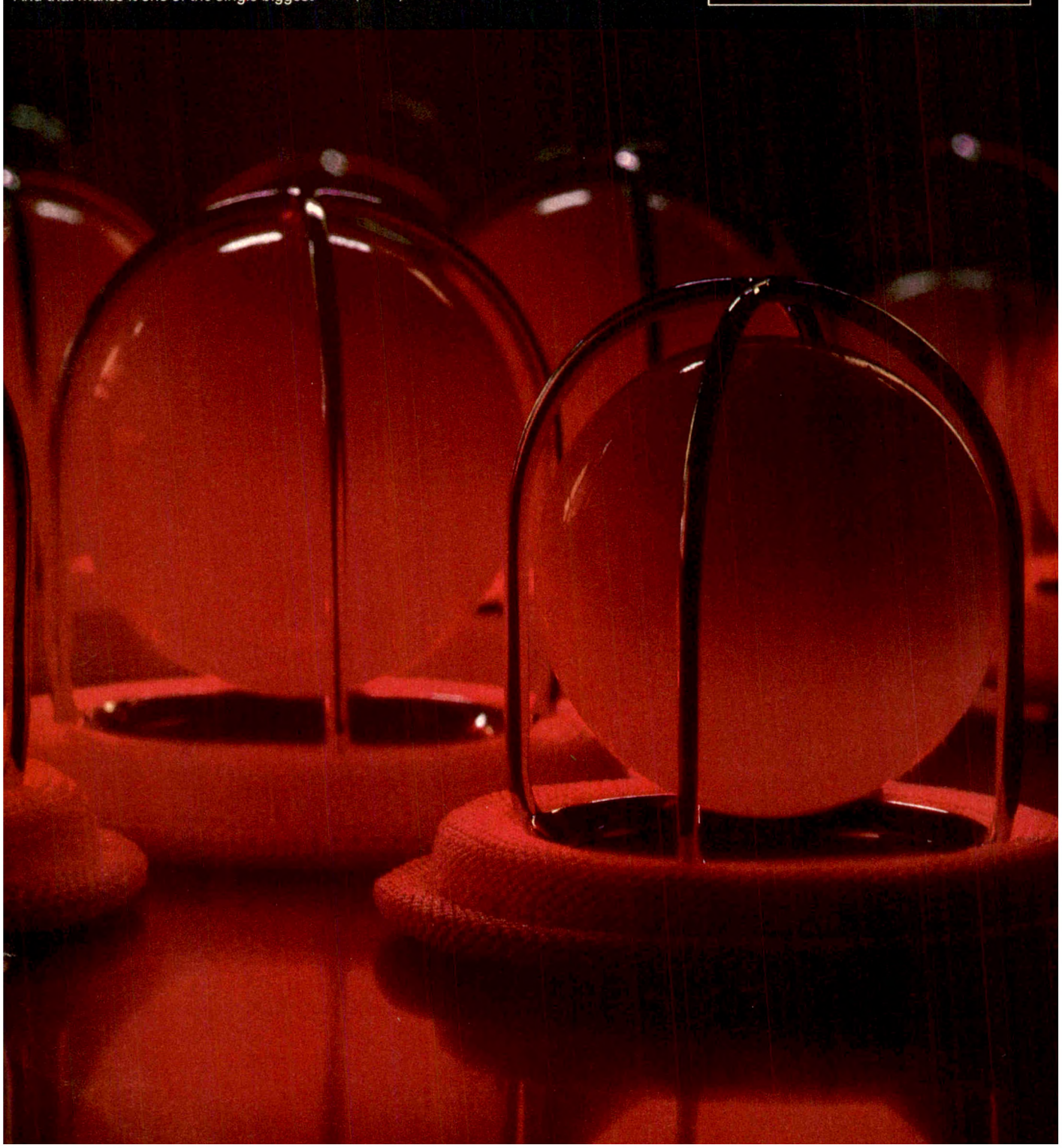

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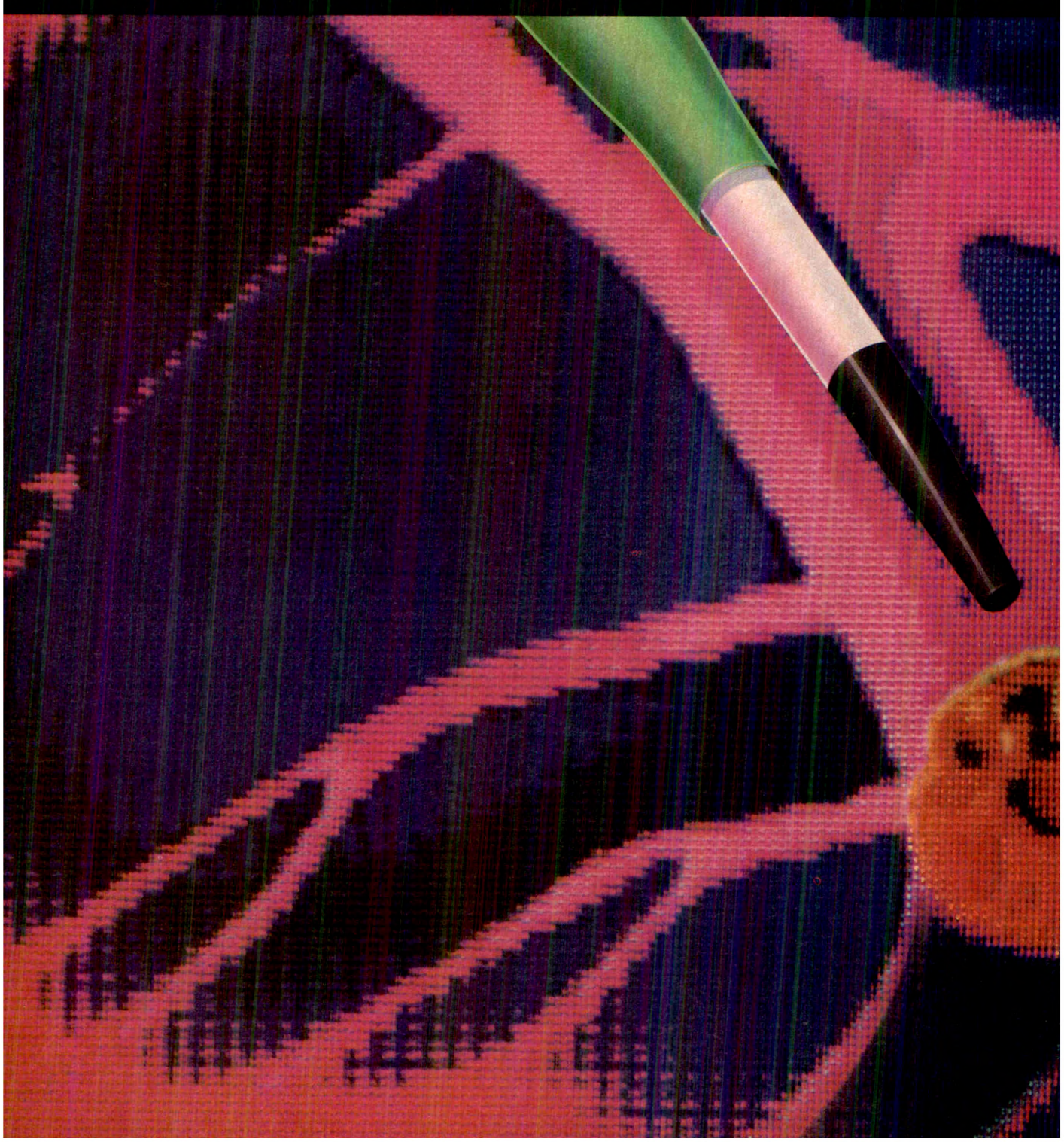

] An atraumatic distal 20 cm for safer vancement into distal locations of the ronary vasculature.
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1. Rentrop, P., et al: "Effects of Nonsurgical Reperfusion on the Left Ventricle in Human Subjects Compared with Conventional Treatment." *American Journal of Cardiology,* 49:1, 1982.
2. Cowley, M., et al: "Effects of Intracoronary Streptokinase in Acute Myocardial Infarction." *American Heart Journal,* 102:1159, 1981.
3. Ganz, W., et al: "Intracoronary Thrombolysis in Evolving Myocardial Infarction." *American Heart Journal,* 101: 4-3, 1981.

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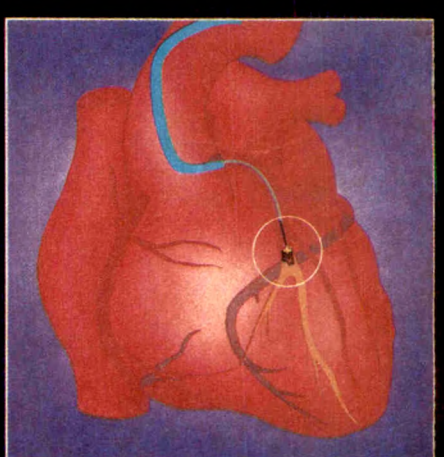

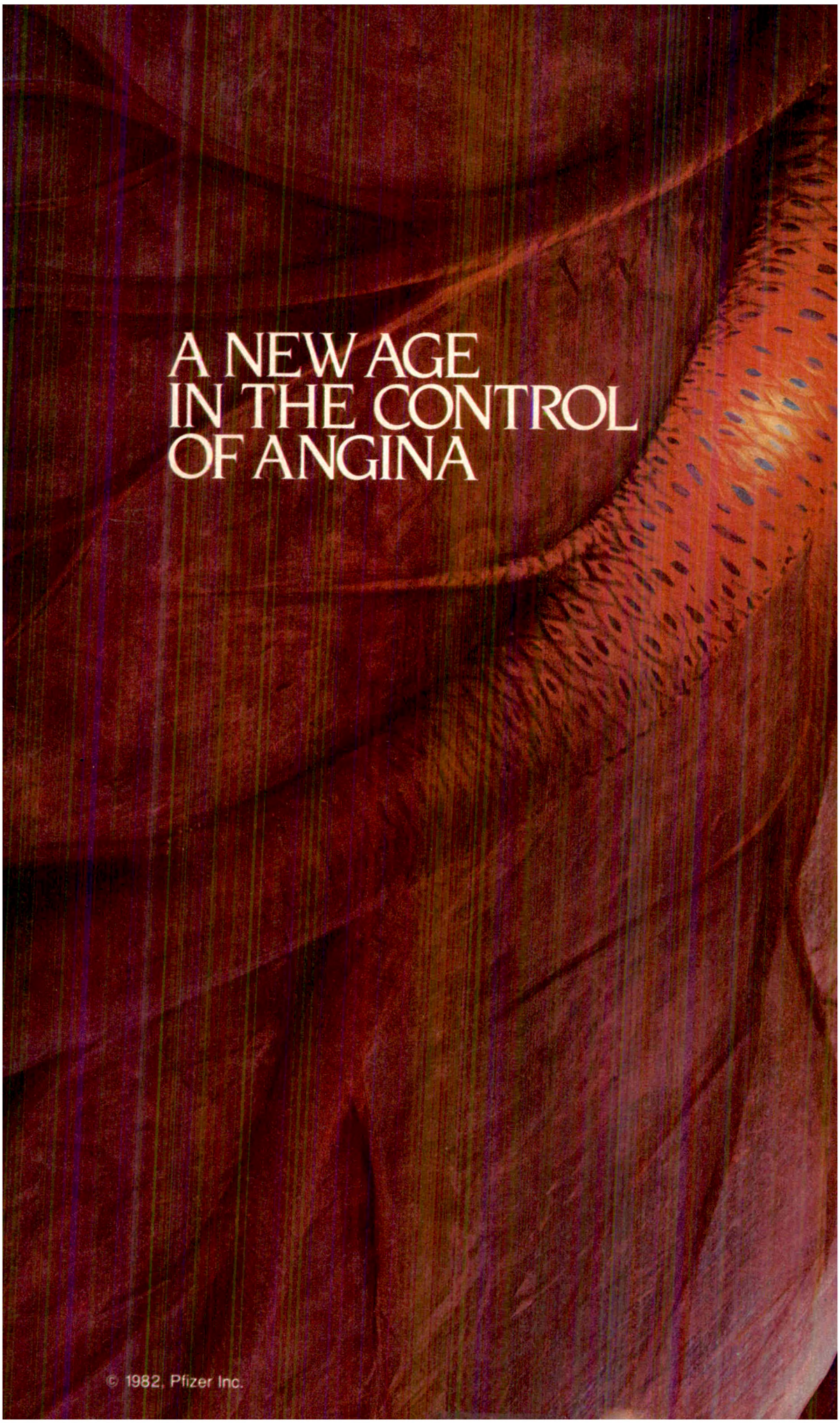

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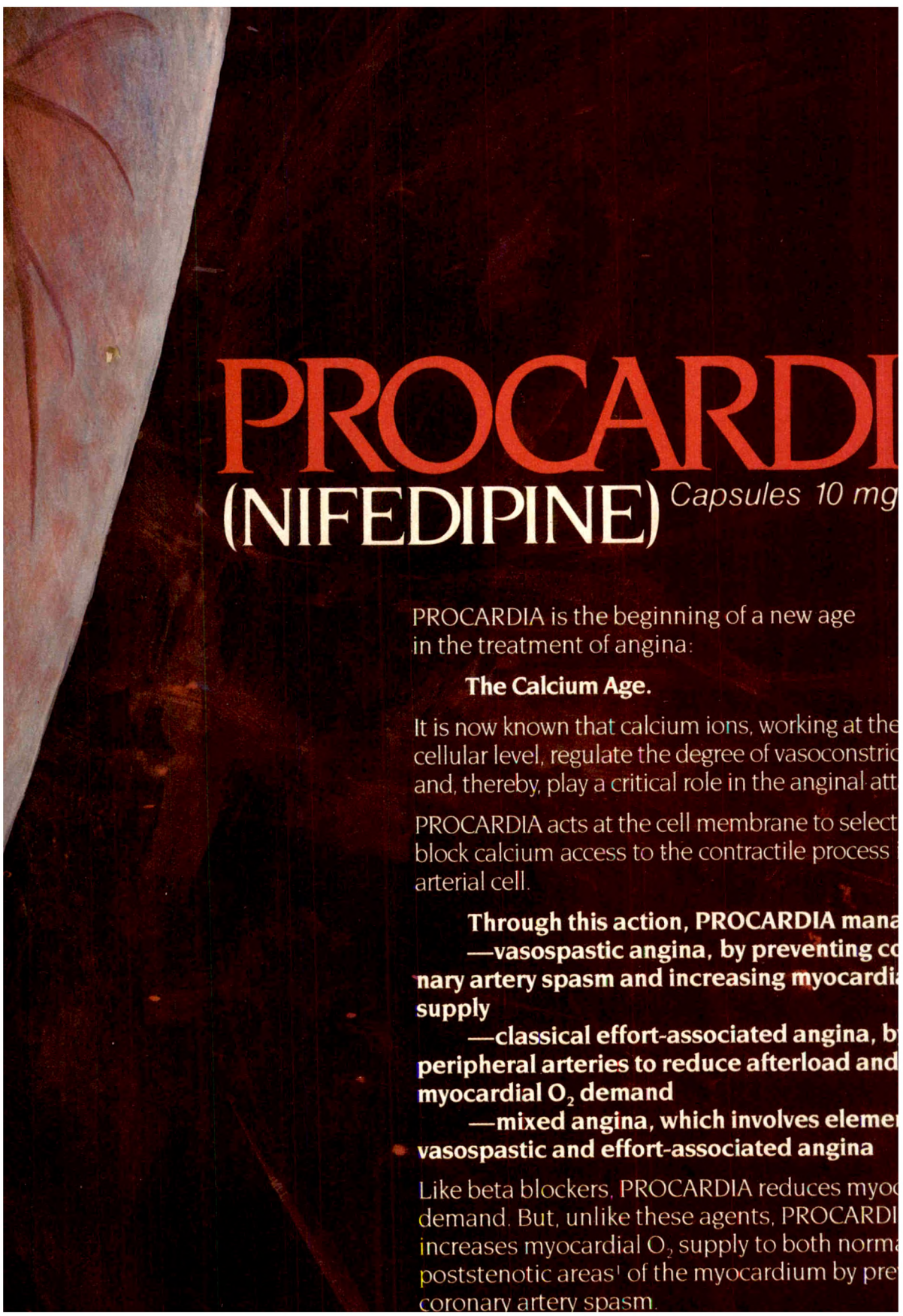
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PROCARDIA is the beginning of a new age
in the treatment of angina:
The Calcium Age.
It is now known that calcium ions, working at the
cellular level, regulate the degree of vasoconstric
and, thereby, play a critical role in the anginal att
PROCARDIA acts at the cell membrane to select
block calcium access to the contractile process
arterial cell.
Through this action, PROCARDIA mana
—vasospastic angina, by preventing co
nary artery spasm and increasing myocardi
supply
—classical effort-associated angina, b
peripheral arteries to reduce afterload and
myocardial O_2 demand
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Like beta blockers, PROCARDIA reduces myoc
demand. But, unlike these agents, PROCARDI
increases myocardial O_2 supply to both norma
poststenotic areas[1] of the myocardium by pre
coronary artery spasm.

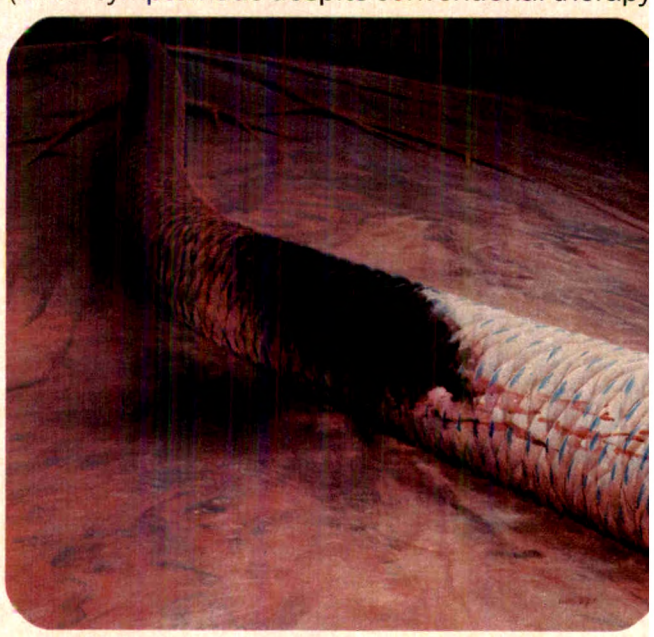
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

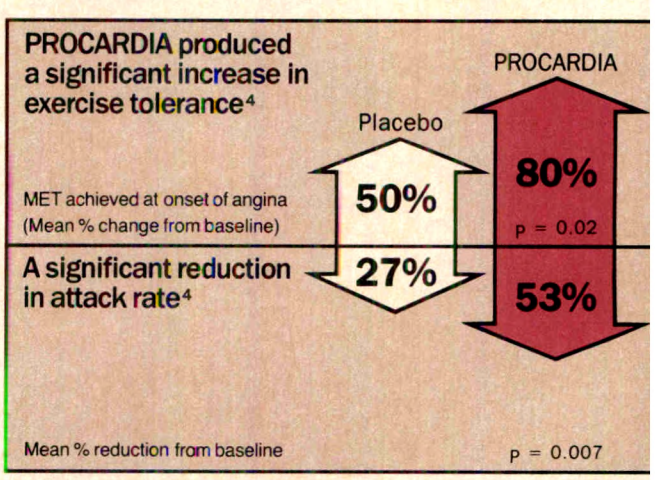
PROVEN EFFECTIVE ACROSS THE SPECTRUM OF ANGINA

Contemporary medical opinion holds that the pathophysiology of angina is a spectrum ranging from pure, fixed atherosclerotic lesion to pure coronary artery spasm. Many patients, however, are believed to have a combination of both lesion and spasm.[2,3]

Angina due to pure fixed lesion can be prevented by reducing oxygen demand. Angina due to coronary artery spasm can be treated by preventing the spasm itself, thereby increasing oxygen supply. With this new understanding of angina, optimal antianginal therapy should provide this dual action: increasing O_2 supply while reducing O_2 demand.

In effort angina*
(when symptomatic despite conventional therapy



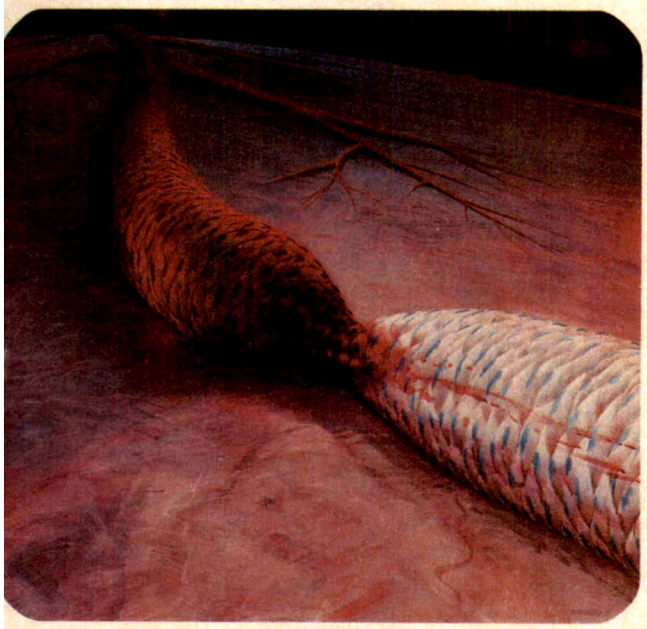


Double-blind, placebo-controlled, crossover 20-week study of 32 patients (27 evaluated for attack rate; 19 for exercis tolerance). Mean PROCARDIA dosage: 51 mg/day.

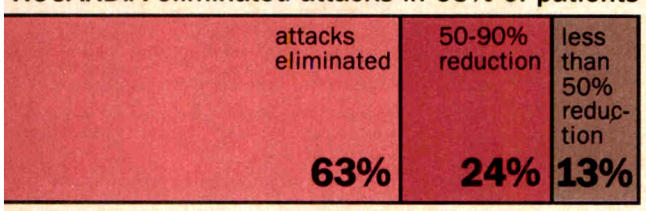
*In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete

Please see PROCARDIA Brief Summary on last page.

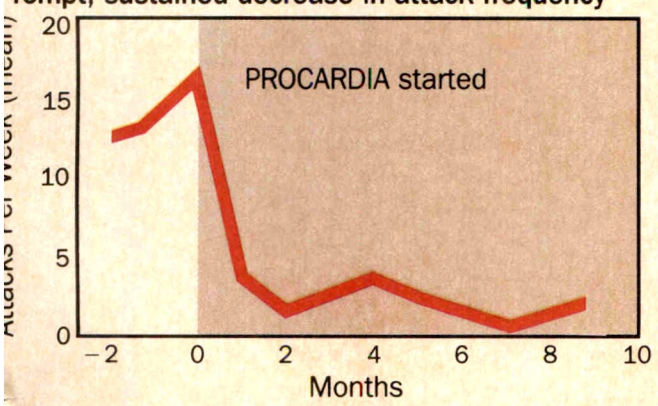
In vasospastic angina



PROCARDIA eliminated attacks in 63% of patients[5]

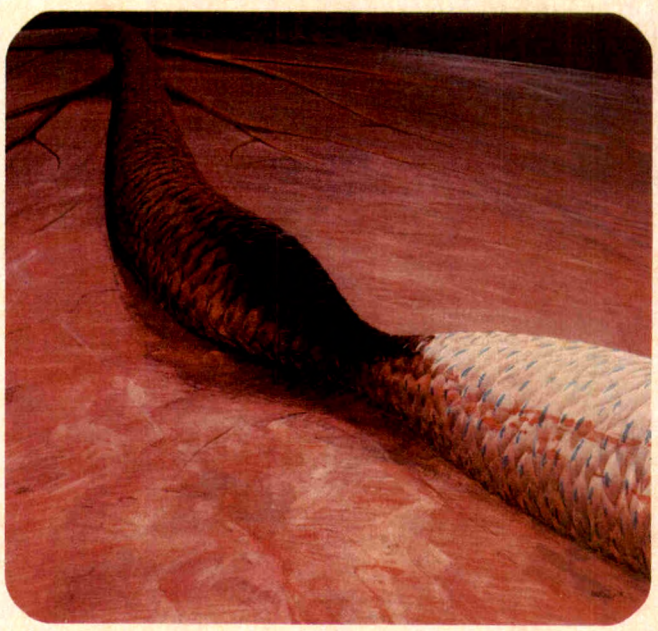


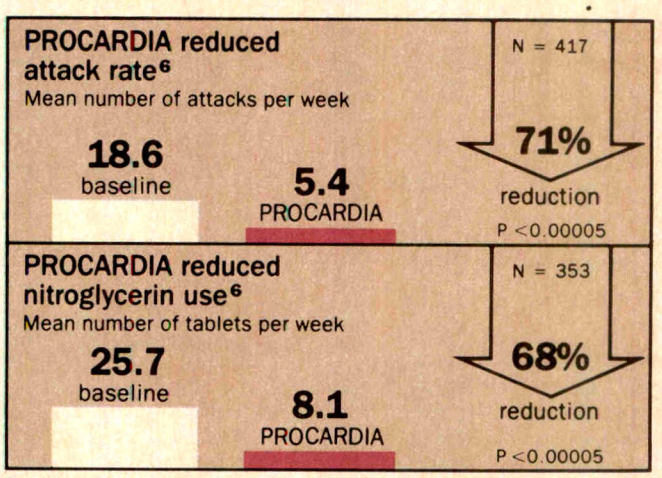
Prompt, sustained decrease in attack frequency[5]



Long-term, open study of 127 patients unresponsive to beta blockers and/or nitrates with symptoms of myocardial ischemia and demonstrated coronary artery spasm. PROCARDIA dosage: 40 to 160 mg/day.

In mixed angina (fixed lesion and spasm)





Studies of patients with mixed angina characterized by pain at rest and effort. Most patients (89%) were initiated on nitrate and/or beta blocker therapy but remained symptomatic. Minimum duration of nifedipine treatment two months. Nifedipine dosage: 30 to 120 mg/day.

PROCARDIA®
THE FIRST ORAL CALCIUM CHANNEL BLOCKER

THE FIRST ORAL CALCIUM CHANNEL BLOCKER FOR THE MANAGEMENT OF ANGINA

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Proven effective when used alone.

Enhanced effectiveness when combined with beta blockers.

Convenient dosing

Start with:	1	10-mg capsule *t.i.d.*
Titrate to:	2	10-mg capsules *t.i.d.*
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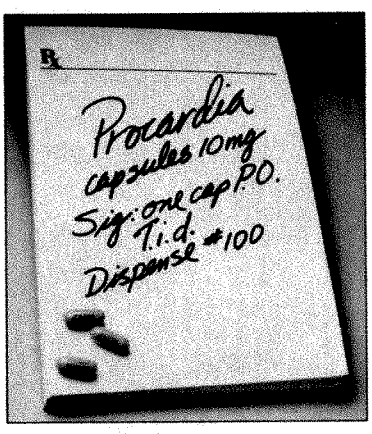

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely. Maximum dose: 180 mg/day

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PROCARDIA® CAPSULES For Oral Use

(nifedipine)

BRIEF SUMMARY

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Increased Angina/Beta Blocker Withdrawal: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Pregnancy: Category C.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA Capsule contains 10 mg of nifedipine. PROCARDIA Capsules are supplied in amber glass bottles of 100 capsules (NDC 0069-2600-66).

The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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Exercise Electrocardiogram, Blood Pressure, and Working Capacity in Young Patients With Valvular or Discrete Subvalvular Aortic Stenosis

FREDERICK W. JAMES, MD, DAVID C. SCHWARTZ, MD, SAMUEL KAPLAN, MD, and STEVE P. SPILKIN, MD

Electrocardiographic changes, blood pressure, and working capacity (total work) were recorded during an upright cycle exercise test in 65 children and young adults (mean age 12 years) with valvular or discrete subvalvular aortic stenosis. All patients had cardiac catheterization, but none had surgical treatment. Controls consisted of 164 normal subjects (mean age 15 years). In the patients, the intervals between the exercise test and cardiac catheterization were 1 month or less in 66%, 2 to 12 months in 28%, and 12 to 24 months in 6%. The patients were classified by resting left ventricular to aortic peak systolic pressure gradient into Groups I (gradient less than 30 mm Hg), II (30 to 49 mm Hg), III (50 to 69 mm Hg), and IV (70 mm Hg or greater).

The mean frequency and magnitude of exercise-induced S-T depression were greater in the patients than in the control subjects ($p < 0.005$) and increased with increasing obstruction in the patients. Mean total work and peak exercise systolic pressure were significantly decreased in the patients with a left ventricular to aortic systolic gradient of 30 mm Hg or greater as compared with the control subjects ($p < 0.03$). An exercise profile consisting of S-T depression of 2 mm or more, and markedly decreased total work and systolic blood pressure were characteristic of the 19 patients (Group IV) with a resting left ventricular to aortic systolic gradient of 70 mm Hg or greater. At least 2 or more components of this exercise profile occurred in 11 (24%) of the 46 patients with a resting left ventricular to aortic systolic gradient less than 70 mm Hg. This study demonstrates that exercise testing reveals serious abnormalities in patients otherwise classified as having trivial or moderate obstruction, and that a properly performed exercise study can be done at minimal risk to the patient.

During controlled exercise, children with serious left ventricular outflow tract obstruction develop significant S-T depression[1–3] suggesting left ventricular subendocardial ischemia. Several investigators[2,3] reported that significant exercise-induced S-T depression indicates a resting left ventricular to aortic peak systolic gradient of 50 mm Hg or more. Recently, Whitmer et al.[4] reported exercise data in children who were surgically treated for aortic stenosis. In that study, significant S-T depression occurred in patients with a resting left ventricular to aortic systolic gradient of less than 50 mm Hg and resolved after successful surgical relief of obstruction. Preliminary studies[5,6] suggest that exercise blood pressure and working capacity are related to resting left ventricular to aortic peak systolic gradient and are important factors in estimating the severity of aortic stenosis.

Since exercise testing is frequently considered in the evaluation of children with aortic stenosis, this study was designed to determine the electrocardiographic changes, blood pressure, and total work during graded cycle exercise in a cross-section of patients with valvular or discrete subvalvular obstruction of varying severity. These data are analyzed according to resting gradient in order to appreciate the abnormal exercise responses associated with progressive obstruction. This study

From Children's Hospital Medical Center, Department of Pediatrics (Cardiology), Cincinnati, Ohio. This study was supported in part by Grant 5 R01 HL 18454-02 and Grant P60 HL 15996-06 from the National Heart, Lung, and Blood Institute of the National Institutes of Health, Bethesda, Maryland; by Grant 76 853 from the American Heart Association; and by the American Heart Association, Southwestern Ohio Chapter. Manuscript received April 21, 1981; revised manuscript received March 23, 1982, accepted April 7, 1982.

Address for reprints: Frederick W. James, MD, Division of Cardiology, Children's Hospital Medical Center, Cincinnati, Ohio 45229.

should improve our understanding of the disease process, improve the selection of patients for cardiac catheterization or surgery, or both, and assist in providing proper guidelines for conducting exercise tests in children with aortic stenosis.

Methods

Patients: Sixty-five patients (52 male and 13 female) between ages 4 and 24 years (mean 12) with valvular (56) and discrete subvalvular (9) aortic stenosis underwent a cycle exercise test using a continuous graded protocol. Physical examination revealed trivial aortic incompetence in 24 patients and mild to moderate in 8. All patients had cardiac catheterization, and aortography or left ventriculography, or both. There was no exercise intervention during cardiac catheterization.

The exercise test was performed within 1 month of cardiac catheterization in 43 patients. When the exercise study followed catheterization, a minimum of 3 to 4 weeks were permitted to elapse before testing, for maximal relief of leg soreness which may follow insertion of catheters in the groin. In the remaining 22 patients, the exercise study and cardiac catheterization were performed within 2 to 12 months in 18 patients, and 12 to 24 months in 4. During the interim between the exercise study and cardiac catheterization, the clinical examination remained unchanged. For those patients requiring surgical relief of left ventricular outflow tract obstruction, only the data from their preoperative exercise test and cardiac catheterization are included.

Control subjects: One hundred sixty-four children and young adults (100 male and 64 female, aged 5 to 33 [mean 15] years) served as controls. All participants had a normal resting physical examination, supine blood pressure, and resting electrocardiogram. Cardiac arrhythmia was not observed in any subject during a 20 to 30 minute period before the exercise test.

Exercise procedure: The continuous exercise cycle protocol described by James et al.[7] was used. The exercise procedure was explained to the patient and parent or guardian, or both, and informed consent was obtained. The exercise test was conducted by a physician who monitored and instructed the patient during the test, and coordinated the recording of certain variables such as heart rate, blood pressure, and the multiple lead electrocardiogram. Two technicians assisted with primary functions of recording the blood pressure and electrocardiogram.

The test was performed on a cycle ergometer (Quinton Instrument, model 845) with a programmer (model 644) enabling automatic progression through the preselected exercise program. A 15 lead electrocardiogram (12 conventional leads plus Frank orthogonal leads X, Y, Z) was recorded using a multichannel recorder (Siemens Mingograf 62). The average of 2 consecutive R-R cycles on the electrocardiogram recorded at a paper speed of 50 mm/s is used for the computation of the heart rate (beats/min). Blood pressure was measured in the right arm of each patient using a programmable air compression cuff system (Narco Biosystem, PE-300) operated by remote control. The guidelines of the Task Force on Blood Pressure Control in Children[8] were followed for selecting the appropriate size compression cuff.

Before exercise, a conventional 12 lead electrocardiogram and Frank orthogonal leads (X, Y, Z) were recorded in the supine and standing positions with and without hyperventilation. Before testing, 3 simultaneous electrocardiographic leads were observed on the oscilloscope for arrhythmia. Heart rate and blood pressure were recorded in the supine position and while sitting on the bicycle ergometer.

During exercise, each patient pedalled at a constant speed (60 to 70 revolutions/min) on the ergometer while the work load increased automatically every 3 minutes. Six electrocardiographic leads (V_1, V_5, V_6, II, X, and Y) were simultaneously recorded every minute. The remaining 9 leads were frequently scanned for changes in the S-T segment. Heart rate was recorded every minute and blood pressure every 1 to 2 minutes. At the peak level of exercise, the electrocardiogram, blood pressure, heart rate, and exercise time were recorded.

Under the protocol, the exercise test was discontinued if 1 or more of the following end points (signs or symptoms) appeared: (1) serious cardiac arrhythmia and conduction disturbance, that is, ventricular tachycardia, premature ventricular complexes greater than 25% of heart rate, supraventricular tachycardia, or induced second or third degree atrioventricular block; (2) S-T depression of 3.0 mm or greater; (3) inappropriate decrease in systolic pressure, that is, 20 mm Hg or greater; (4) exhaustion; and (5) chest pain, dizziness, or pallor.

Cardiac catheterization and angiography: While the patient was sedated in the supine position, the resting left ventricular to aortic systolic gradient was measured from a withdrawal pressure tracing across the obstructed outflow area. Cardiac output was measured in 86% of patients by either the Fick, thermodilution, or cardiogreen method in close sequence to the recording of pressure and before angiography. The anatomy of the valvular and subvalvular areas was determined from the aortogram and left ventriculogram. The severity of aortic incompetence was determined from an interpretation of the aortogram as described by Sellers et al.[9] In this study, 1+ regurgitation is considered trivial and 2+, moderate aortic incompetence.

Data analysis: Total work was calculated as the sum of the products of workload (in kilogram-meters/minute) and exercise time (in minutes) at each level reached in the exercise program. The electrocardiogram was analyzed for (1) S-T depression of 1.0 mm or greater for a duration of at least 60 ms in any lead at peak performance (the baseline for measuring S-T depression is defined as a straight line through the P-R or P-Q junction of 3 to 5 consecutive P-QRS-T complexes)[7]; (2) distribution of the S-T depression; and (3) arrhythmia.

The patients were subdivided into 4 groups according to the magnitude of the resting left ventricular to aortic peak systolic pressure gradient as follows: (1) 29 mm Hg or less (mean 20) in 16 patients (11 male and 5 female) aged 7 to 24 years; (2) 30 to 49 mm Hg (mean 37) in 14 patients (11 male and 3 female) aged 8 to 16 years; (3) 50 to 69 mm Hg (mean 56) in 16 patients (15 male and 1 female) aged 5 to 24 years; and (4) 70 mm Hg or more (mean 105) in 19 patients (15 male and 4 female) aged 4 to 19 years.

Statistical analysis: Mean (± standard error) values for peak exercise heart rate, total work, blood pressure, and magnitude of S-T depression were calculated. The mean values for total work and peak exercise systolic blood pressure were adjusted for the confounding effect of sex, height, and rate of work using analysis of covariance.[7,10] The significance of the difference of means among the control subjects and patient groups were determined by the technique of multiple comparisons. Other mean (± standard error) differences were analyzed by analysis of variance. The frequency of S-T depression of 1 mm or greater was analyzed using the chi-square test.

TABLE I Distribution of S-T Depression of 1 mm or Greater and S-T Segment Slope at Peak Exercise in Control Subjects and Patients With Aortic Stenosis

	n	S-T Segment Slope*			
		Depression	Upward	Horizontal	Downward
Control subjects	164	19	17	2	. . .
Patient groups					
I	16	6	3	2	1
II	14	9	4	5	. . .
III	16	7	3	2	2
IV	19	17	5	10	2

* The S-T segment slope was recorded in the electrocardiographic lead with the greatest amount of S-T depression.

Results

Clinical Data

Group I (resting gradient less than 30 mm Hg): Twelve (75%) of the 16 patients were asymptomatic. Sporadic complaints of chest pain, tiredness, dizziness, and palpitation occurred in the remaining 4 patients. After an interim of 5 years, these 4 patients were asymptomatic and continued to have signs of mild aortic stenosis and trivial to moderate aortic valve incompetence on physical examination.

The resting electrocardiogram was normal in 7 (44%), revealed left ventricular hypertrophy by voltage criteria in 4 (25%), questionable left ventricular hypertrophy in 4 (25%), and left axis deviation in 1 (6%). The chest radiograph was normal in 13 patients (81%), and revealed mild cardiac enlargement in 1 (6%) and a dilated ascending aorta in 2 (13%).

The mean resting systolic gradient was 20 mm Hg with a mean left ventricular pressure of 127/9 and aortic pressure of 107/67. Trivial aortic valve incompetence was present in 9 (56%) and moderate in 2 (13%). The aortic valve was tricuspid in 13, bicuspid in 2, and undetermined in 1 by angiography.

Group II (resting gradient 30 to 49 mm Hg): Eleven (79%) of the 14 patients were asymptomatic and 3 complained of either chest pain or tiredness. The resting electrocardiograms were normal in 9 (64%), and revealed left ventricular hypertrophy in 4 (29%) and questionable left ventricular hypertrophy in 1 (7%). The chest radiograph was normal in 11 (79%), and revealed mild cardiomegaly in 1 (7%) and a dilated aorta in 2 (14%). The mean resting systolic gradient was 37 mm Hg with a mean left ventricular pressure of 137/8 and aortic pressure of 100/66. Trivial aortic valve incompetence was present in 5 (36%) and moderate in 3 (21%). The aortic valve was tricuspid in all patients.

Group III (resting gradient 50 to 69 mm Hg): Ten (62%) of the 16 patients were asymptomatic and 6 (38%) complained of either chest pain, dizziness, or tiredness. The resting electrocardiogram was normal in 4 (25%) and revealed left ventricular hypertrophy in 8 (50%), abnormal S-T segments and T waves in 2 (12.5%) and left axis deviation in 2 (12.5%). The chest radiograph was normal in 8 (50%) and revealed cardiomegaly in 6 (38%) and a dilated ascending aorta in 2 (12%). The mean resting systolic gradient was 56 mm Hg with a mean left ventricular pressure of 163/12 and an aortic pressure of 107/73. Trivial aortic valve incompetence was present in 3 (19%) and moderate in 3 (19%). The aortic valve was tricuspid in 15 patients and bicuspid in 1.

Group IV (resting gradient 70 mm Hg or greater): Five (26%) of the 19 patients denied having symptoms, and 14 (74%) complained of tiredness, chest pain, syncope, or a combination of these. The resting electrocardiogram was normal in 6 (32%) and revealed left ventricular hypertrophy in 11 (58%) and questionable left ventricular hypertrophy in 2 (11%). The chest radiograph was normal in 12 (63%), and revealed cardiomegaly in 5 (26%) and a dilated ascending aorta in 2 (11%). The mean resting systolic gradient was 105 mm Hg with a mean left ventricular pressure of 215/13 mm Hg and aortic pressure of 111/75 mm Hg. Trivial aortic valve incompetence was present in 7 patients (37%). The aortic valve was tricuspid in all patients.

Exercise Data

Electrocardiography (Table I): Significant S-T depression occurred more frequently in the patients than in the normal control subjects ($p < 0.005$). The percentages of exercise-induced S-T depression of 1.0 mm or greater were 38% (6 of 16 patients) in Group I, 64% (9 of 14) in Group II, 44% (7 of 16) in Group III, and 89% (17 of 19) in Group IV. For the 39 patients with S-T depression of 1.0 mm or greater, the mean decreases in the electrocardiographic leads showing the greatest amount of S-T segment change at peak exercise were 1.5, 2.0, 1.8, and 2.4 mm in Groups I, II, III, and IV, respectively (Fig. 1). The S-T segment was horizontal in 49%, upward sloping in 38%, and downward sloping in 13% of the 39 patients with significant S-T depression. The horizontal S-T segment was most common in Group IV, whereas the upward sloping S-T segment was most common in Group I.

Significant exercise-induced S-T depression occurred in the left precordial leads (V_5 and/or V_6) in 35 (90%) of the 39 patients, but was isolated to the left precordial leads in 21 patients (54%). Significant S-T depression was recorded in the inferior leads (II, III, aVF) in 18 (46%) of the 39 patients, but was isolated to

these leads in 4 patients (10%). Fourteen (36%) patients had significant exercise-induced S-T depression in both left precordial and inferior leads. S-T depression of 1 mm or more was recorded in 2 or more leads in 22 patients (56%). In 32 patients (82%), significant exercise-induced S-T depression was detectable in lead V_5. Four patients (6%) had premature ventricular complexes, which necessitated discontinuing the test in 1. In this patient, the premature beats were multifocal with a frequency of more than 25% of the heart rate. In the 4 patients, the occasional ventricular arrhythmia had either a right or left bundle branch block pattern.

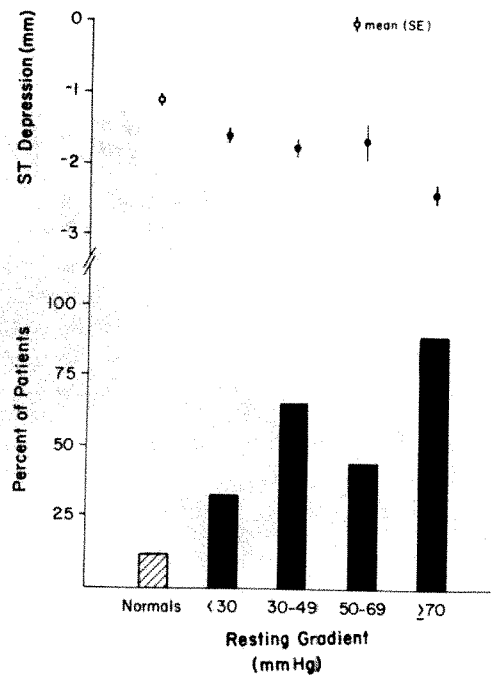

FIGURE 1. Exercise-induced S-T depression in normal subjects and patients with aortic stenosis. The mean frequency and magnitude of S-T depression increases in the patients with an increasing resting left ventricular to aortic systolic pressure gradient. SE = standard error.

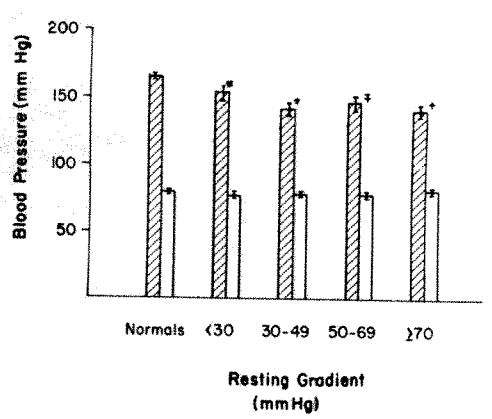

FIGURE 2. Mean (± standard error) peak exercise blood pressure in normal subjects and patients with aortic stenosis. Mean (± standard error) peak systolic pressure is adjusted for body size (height), sex, and work load. Adjusted mean systolic pressure (**hatched bars**) in the patients is significantly lower than normal. Mean (± standard error) peak diastolic pressure (**clear bars**) did not differ significantly among the normal subjects and patients. Levels of significance: *$p < 0.03$; †$p < 0.0001$; ‡$p < 0.0002$.

In the control subjects, the incidence of S-T depression of 1 mm or greater was 12% at peak exercise with a mean magnitude of depression of 1.1 mm. In these patients with S-T depression of 1 mm or greater, the slope of the S-T segment was upward in 89% and horizontal in 11%. Occasional ventricular arrhythmia occurred in 2 (1%) subjects during exercise.

Blood pressure: For each group, the mean (± standard error) pre-exercise supine systolic pressure adjusted for sex and body size (height) was similar to that of the control subjects ($p > 0.1$) (Fig. 2). Also, the mean pre-exercise systolic pressure while sitting on the bike did not differ significantly from that of the control subjects. Mean (± standard error) pre-exercise diastolic pressures in the supine and sitting positions were not significantly different from normal ($p > 0.1$).

During exercise, mean (± standard error) peak-exercise systolic pressures for the patient groups and control subjects were adjusted for the confounding effect of sex, body size (height), and rate of work.[7] In Group I, the adjusted mean (± standard error) peak-exercise systolic pressure (155 ± 4 mm Hg) did not differ significantly from normal ($p > 0.1$). For the other groups, the adjusted mean (± standard error) peak-exercise systolic pressures were 142 ± 5, 151 ± 5, and 148 ± 4 mm Hg for Groups II, III, and IV, respectively, as compared with 161 ± 1 mm Hg for the normal subjects ($p < 0.03$). In all patient groups, mean peak-exercise diastolic pressure was similar to normal ($p > 0.1$).

For each patient in Groups I and II, systolic pressure increased above the pre-exercise level during the exercise test. Systolic pressure during exercise was equal to or less than the pre-exercise systolic pressure in 7 patients, 1 (6%) in Group III and 6 (32%) in Group IV.

Heart rate: Mean (± standard error) pre-exercise heart rates adjusted for sex and body size (height) were 75 to 87 beats/min in the patient groups and normal subjects ($p > 0.1$). Mean (± standard error) peak exercise-heart rates were 190 ± 4 beats/min in Group I, 188 ± 4 in Groups II and IV, and 194 ± 1 in normal subjects. The mean peak heart rate (183 ± 4) in Group III differed significantly from normal ($p < 0.008$) but exceeded 180 beats/min, implying satisfactory effort during the study.

Working capacity: Mean (± standard error) total work (in kilogram-meters) adjusted for the confounding effect of sex and body size (height) was 5,893 ± 858 for Group I, 4,973 ± 925 for II, 3,596 ± 89 for III, 3,851 ± 822 for IV, and 7,600 ± 273 for normal subjects (Fig. 3). Groups II to IV differed significantly from normal with a level of significance of $p < 0.007$, < 0.0001, and < 0.0001, respectively. The adjusted mean (± standard error) highest rate of work (maximal power output, in kilogram-meters/minute) achieved during the test was 776 ± 50 in Group I, 742 ± 54 in II, 590 ± 53 in III, 591 ± 48 in IV, and 878 ± 16 in normal subjects. The level of

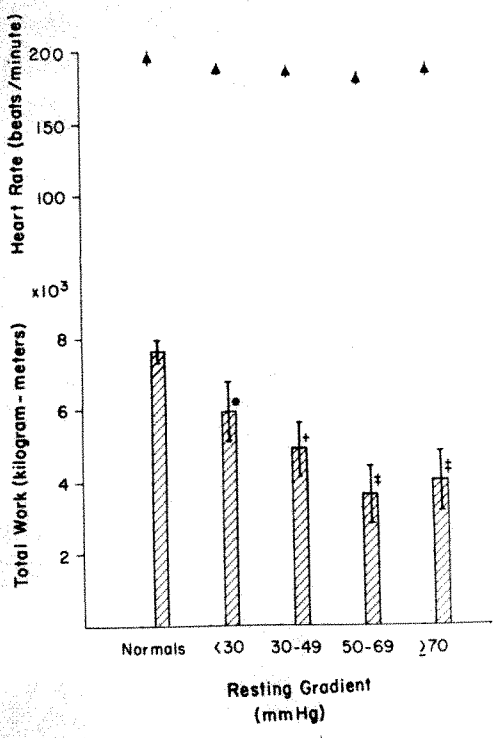

FIGURE 3. Mean (± standard error) working capacity (total work) and peak exercise heart rates in normal subjects and patients with aortic stenosis. After an adjustment for body size (height) and sex, mean (± standard error) total work is significantly decreased in the patients compared with the control subjects. Mean peak exercise heart rates exceeded 180 beats/min in all patient groups and normal subjects. Levels of significance: *p <0.04; †p <0.003; ‡p <0.001.

significance for the difference in maximal power output between each group (I to IV) and normal was $0.06 > p > 0.05$, $p < 0.007$, $p < 0.0001$, and $p < 0.0001$, respectively.

Decreased systolic pressure, total work, and S-T depression: Further analysis was performed to determine the frequency of decreased total work and exercise systolic pressure of −2 standard deviations or more from a normal mean,[7] and S-T depression of 2 mm or greater indicating marked subendocardial ischemia within each patient group (I to IV). S-T depression of 2 mm or more occurred in 74, 31, and 21% in patients of Groups IV, III, and II, respectively. A decreased systolic pressure during exercise and total work occurred most frequently in Group IV at a frequency of 52 and 37%, respectively (Table II). Two or more of the abnormal exercise responses occurred in 47, 25, 29, and 6% of patients in Groups IV, III, II, and I, respectively.

Discussion

This study reveals an increased frequency and magnitude of S-T depression, altered systolic pressure, and decreased working capacity during controlled exercise in children and young adults with valvular or discrete subvalvular aortic stenosis of varying severity. The most abnormal exercise responses occurred in patients with a resting left ventricular to aortic systolic gradient of 70 mm Hg or greater. One or more of these exercise responses was markedly abnormal in 16 of 46 (35%) and 2 or more in 8 of 46 (17%) patients with a left ventricular to aortic systolic gradient less than 70 mm Hg.

TABLE II Frequency of S-T Depression 2 mm or Greater, Systolic Pressure, and Total Work of −2 Standard Deviations or Less at Peak Exercise in Patients

	Group			
	I	II	III	IV
Number	16	14	16	19
S-T depression	. . .	3 (21%)	5 (31%)	14 (74%)
↓ Systolic pressure	4 (25%)	6 (43%)	4 (25%)	10 (52%)
↓Total work	4 (25%)	1 (7%)	5 (31%)	7 (37%)

↓ = decreased.

Exercise Electrocardiogram

Significance: The clinical significance of S-T depression of 1 mm or greater in patients with aortic stenosis is related to other abnormal exercise responses. In our patients with aortic stenosis, S-T depression of 1 mm or greater with normal work and blood pressure at peak exercise suggests mild obstruction with a resting left ventricular to aortic gradient of less than 30 mm Hg. Further, S-T depression of 1 mm or greater with abnormal work and blood pressure at peak exercise suggests significant obstruction with a resting left ventricular to aortic gradient above 30 mm Hg. For healthy children, S-T depression of 1 mm or greater with normal work and blood pressure at peak exercise appears of no clinical significance.

Mechanism: The mechanism for the S-T depression during exercise in the patients with aortic stenosis is thought to be related to an imbalance between myocardial oxygen supply and demand, producing left ventricular subendocardial ischemia. In the control subjects, the mechanism is unclear, but we speculate that strenuous exercise may produce an imbalance between myocardial oxygen supply and demand during the growing period, producing a transient "physiologic" ischemia. Further investigation including longitudinal studies are needed to improve our understanding of the occurrence of S-T depression during exercise in healthy children.

Frequency and predictive value: The frequency of exercise-induced S-T depression of 1 mm or more in our population differed from the studies of Halloran[2] and Chandramouli et al.,[3] who reported that exercise-induced S-T depression of 1 mm or greater indicated a resting left ventricular to aortic systolic gradient greater than 50 mm Hg. In our study, 14 patients with a systolic gradient less than 50 mm Hg had significant exercise-induced S-T depression and 10 patients with a resting systolic gradient greater than 50 mm Hg had no S-T depression during exercise. Using the criteria reported by Halloran,[2] each of the 14 patients had significant exercise-induced S-T depression despite having a resting systolic gradient of less than 50 mm Hg. Simi-

larly, the criteria reported by Chandramouli et al.,[3] which require the S-T segment to be depressed for 80 ms below the baseline, identified significant S-T depression in 11 of the 14 patients. The remaining 3 patients had S-T depression of 1 mm for only 60 ms below the baseline. In contrast to the reported findings of Halloran and Chandramouli, our data do not support using S-T depression to predict the presence of a resting left ventricular to aortic systolic gradient above or below 50 mm Hg in patients. Any further comparison between our study and the series reported by Halloran,[2] Chandramouli,[3] and their co-workers becomes increasingly difficult because of the insufficient data for matching working intensity and the different end points used to discontinue the exercise test.

Factors affecting variability and frequency of S-T depression: Our results suggest that subendocardial ischemia of varying degrees occurs during controlled exercise in patients with aortic stenosis. Further, the degree of ischemia varies in patients having the same or similar resting systolic gradients. The variability may be related to an increased systolic gradient during exercise.[1,11,12] These patients with similar or mild obstruction at rest may have a significantly increased systolic gradient during exercise, causing left ventricular subendocardial ischemia. Since intracardiac pressures were not measured during exercise, this explanation is not confirmed.

Another consideration related to the variability and high frequency of positive S-T depression in patients with a gradient less than 70 mm Hg is the stage of developed hypertrophy at the time of the exercise study. The major stimuli for developing cardiac hypertrophy in this young population are growth and the severity of left ventricular outflow tract disease.[13] The stage of this development probably varies in patients who have so-called mild or similar resting systolic gradients.

The stage of developed hypertrophy and the adaptation to increased cardiac work potentially influence a patient's response to strenuous exercise. In 20 patients who had serial exercise testing between 1 and 5 years, the mean S-T depression in 7 patients (35%) decreased from 1.5 mm during the initial study to 0.5 mm during the follow-up study while performing the same or greater amounts of work. Exercise responses including S-T segment changes are highly reproducible on serial examinations in normal children who have not had physical training and any significant changes in body size.[7] The resolution of the S-T segment in these patients during the longitudinal follow-up may reflect improved adaptation to increased cardiac work, and an improved balance between supply oxygen and demand for oxygen of the myocardium. The S-T depression in the remaining 13 patients increased or was unchanged at the follow-up study. These preliminary findings suggest that significant exercise-induced S-T depression may resolve in certain young patients who have not had the benefit of surgical treatment.

Location of S-T depression: Significant S-T depression was widely distributed (left precordial and inferior leads) in 36% of the patients, suggesting diffuse acute subendocardial ischemia of the left ventricle. Exercise-induced S-T depression was isolated to the left precordial leads (V_4, V_5, and/or V_6) in 54% and to the inferior lead (aVF) in 10%, suggesting regional acute subendocardial ischemia.

The isolated S-T segment depression perhaps reflects the disproportionate increase in wall thickness from pressure-overload[13] of the left ventricle. Experimental data in dogs with left ventricular hypertrophy from aortic banding above the coronary arteries reveal regional maldistribution of myocardial blood flow during exercise.[14,15] The clinical and experimental data suggest that regional subendocardial ischemia probably occurs during exercise in young patients with aortic stenosis and suspected normal coronary arteries.

Blood pressure: Preliminary studies reveal an abnormal rise in systolic pressure occurring in patients with aortic stenosis. Riopel et al.[6] suggest that the difference between exercise systolic and pre-exercise systolic pressure is related to the severity of aortic stenosis. We observed a lower than normal exercise systolic pressure in each of the four patient groups. After an adjustment for sex, body size (height), and rate of work, the difference between the control subjects and patients did not change significantly with increasing gradient. Furthermore, 6 of 19 (32%) patients with a left ventricular to aortic systolic gradient greater than 70 mm Hg had elevated systolic or diastolic pressures, or both.

Mechanism of low exercise systolic pressure: Preliminary data from our laboratory suggest that the mechanism for an abnormally low exercise systolic pressure in patients with a left ventricular to aortic systolic gradient less than 70 mm Hg is a prolonged electromechanical systole.[16] Since the duration of the systole is increased in obstruction,[16] normal or elevated exercise systolic pressure in patients would imply an abnormality of more than one of the determinants of systolic pressure (that is, rate of ejection, stroke volume, and vascular resistance). We suspect that systemic vascular resistance is elevated in patients who have severe obstruction and a normal or elevated exercise blood pressure.

In our study, the systolic pressure during exercise was commonly above the pre-exercise level, but often did not reach the expected level for body size and intensity of work. The exercise systolic pressure fell below or was equal to the pre-exercise value in 6 patients with a left ventricular to aortic systolic gradient above 70 mm Hg. At the same time, the patients had severe S-T depression and the other 3 had chest pain. A fall or lack of rise in systolic pressure during exercise suggested critical obstruction to the left ventricle with a severe compromise in cardiac performance. This response in systolic pressure during exercise was an indication to discontinue the study.

Working Capacity

The amount of work accomplished during the exercise test was inversely related to the resting left ventricular to aortic systolic gradient while mean peak heart

rate exceeded 180 beats/min in each patient group. The exercise test was stopped in 16 patients (25%) because of S-T depression of 3 mm or greater or a fall or lack of rise in exercise systolic pressure, or both, without exercise-induced symptoms. When these 16 patients were omitted from the analysis, total work remained significantly below normal in Groups II, III, and IV ($p < 0.02$, < 0.003, and < 0.007, respectively). In the majority of patients significant abnormal responses were observed during exercise before any symptoms or signs of distress occurred. The quantification of these abnormal changes for known levels of work reveals the severity of the aortic stenosis and the potential benefit of controlled exercise testing in the clinical management of these young patients.

Clinical Symptoms

Twenty (31%) of 65 patients had chest pain, dizziness, or syncope by clinical history as compared with 6 (9%) patients developing symptoms (chest pain or dizziness) during the exercise test ($p < 0.016$). The disparity between the history and the results of the exercise test demonstrate that serious abnormalities reflecting a major compromise in cardiac performance may precede clinical symptoms. In the uncontrolled state, outside the laboratory, the patient is unaware of early abnormalities of myocardial performance and perfusion and may continue physical activity until these abnormalities produce symptoms.

Interpretation of Exercise Tests and Recommendations

A common practice for determining the severity of aortic stenosis is to measure the left ventricular to aortic systolic gradient at rest with or without simultaneous measurement of cardiac output. Although treatment is not standardized, patients with a left ventricular to aortic systolic gradient exceeding 70 mm Hg and in some instances of less magnitude[4] are generally recommended for surgical relief of the obstruction.

This study identifies patients previously judged to have mild obstruction whose exercise response simulates that found in patients with a left ventricular to aortic systolic gradient of 70 mm Hg or greater. We previously showed that patients having marked S-T depression and decreased total work or exercise systolic pressure, or both, benefit from surgery.[4] After surgery, the improvement in exercise responses may take several months and is partly related to favorable changes in oxygen transport, myocardial performance, and perfusion.

Patients with a slightly abnormal exercise response should be followed up to determine the persistence or progression of the abnormal responses. Progression of abnormal changes during longitudinal follow-up indicates progressive disease and warrants an evaluation by cardiac catheterization and possibly surgical treatment. Although measurement of the gradient remains essential for identifying severe left ventricular outflow tract obstruction, this study demonstrates that exercise testing reveals serious abnormalities of left ventricular performance and perfusion in patients otherwise classified as having moderate or even trivial obstruction.

Safety: This study expands the data base demonstrating that exercise testing can be performed at low risk in children with significant aortic stenosis. A satisfactory system for monitoring several electrocardiographic leads and blood pressure, particularly systolic pressure, is mandatory. Further, properly trained personnel including a physician to evaluate and interpret signs, symptoms, and exercise responses are required to increase the yield and safety of the exercise test.

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Mechanism of Acquired Right Ventricular Outflow Tract Obstruction in Patients With Ventricular Septal Defect: An Angiocardiographic Study

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Right ventricular outflow tract obstruction can complicate the natural history of patients with isolated ventricular septal defect. Although numerous pathologic mechanisms may be responsible for this phenomenon, it is less clear what the frequency is of each of these mechanisms in any cohort of patients studied in a single institution. We identified 20 patients with isolated ventricular septal defect from 1970 to 1981 who acquired a right ventricular outflow tract gradient of 25 mm Hg or more. They ranged in age at the initial catheterization investigation from 4 days to 23 months and at the subsequent study from 13 months to 8 years. Angiographically, 2 mechanisms were implicated in the 20 patients. Hypertrophy of right ventricular anomalous muscle bundles was identified in 19 of the 20 while hypertrophy of a malaligned infundibular septum (that is, classic tetralogy type) was identified in only 1 patient. These data indicate that acquired right ventricular outflow tract obstruction is rarely of the classic tetralogy type.

It is well known that right ventricular outflow tract obstruction may be an acquired phenomenon in some patients with ventricular septal defect and that it can irrevocably alter the patient's natural history. Since the report of Gasul et al.[1] in 1957 on the development of infundibular obstruction in patients with a ventricular septal defect and the subsequent transformation of their conditions into the cyanotic or acyanotic types of "tetralogy of Fallot," a large body of literature has accumulated concerning the incidence and potential mechanisms of this occurrence. Indeed, the report of Weidman et al.[2] on the Joint Study on Congenital Heart Disease suggests that the incidence of acquired right ventricular outflow tract obstruction is about 3%,[3] while the study of Corone et al.[4] suggests a somewhat higher incidence of 7%. A number of small series and case reports have examined the mechanisms of this acquired right ventricular outflow tract obstruction in patients with ventricular septal defect. Although multiple mechanisms have been implicated, there appear to be primarily 2 mechanisms by which right ventricular outflow tract obstruction and ventricular septal defect can be acquired: (1) hypertrophy of right ventricular anomalous muscle bundles, and (2) hypertrophy of a malaligned (anterosuperiorly deviated) infundibular septum as seen in the tetralogy of Fallot malformation. The purpose of our study is to document angiographically the mechanism responsible for acquired right ventricular outflow tract obstruction in 20 patients with ventricular septal defect studied in 1 institution.

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Nomenclature

Ventricular septal defect: There is no unanimity regarding the nomenclature of ventricular septal defect. We will utilize in this study the nomenclature advocated by Soto et al.[5] Again, this is an angiographic study, and we will attempt to define the ventricular septal defect as membranous (or perimembranous), muscular, or subarterial.

A perimembranous ventricular septal defect is one involving the membranous septum and extending into the contiguous muscular septum. Part of the rim of the defect is formed by the central fibrous body. This defect may extend into the inlet, trabecular, or infundibular portions of the septum.

A muscular ventricular septal defect has pure muscular rims and may be located in the inlet, trabecular, or infundibular portions of the ventricular septum.

A subarterial ventricular septal defect has a totally deficient infundibular septum so that the aortic and pulmonary valves are contiguous in the root of the defect.

Various terms have been used to characterize the mechanism considered responsible for acquired right ventricular outflow tract obstruction. Thus, it may therefore be difficult to ascertain the true morphologic basis for such obstruction. Terms such as *prominent crista supraventricularis*,[6,7] *low infundibular stenosis*

with infundibular chamber,[6] *narrow and hyperdynamic infundibulum,*[6,8] *anomalous muscle bundles,*[9,10] and double-chambered right ventricle[11] are often encountered and because of their imprecision may be confusing. We have tried to be very specific in our identification and distinction between true tetralogy anatomy (malalignment between infundibular septum and trabecula septomarginalis) and nontetralogy-like mechanisms.

Anomalous muscle bundles: Anomalous right ventricular muscle bundles may be considered an abnormally positioned and hypertrophied moderator band. As such, they can occur in a high or low position, depending on the site of insertion of the moderator band and on the inclination of the moderator band itself. If the insertion of the moderator band on the septal band is in a higher and more posteromedial position, the anomalous muscle bundle will be closer to the inlet of the right ventricle. There is a continuum of possible points of insertion of the moderator band onto the septal band.[10,11]

The angiographic diagnosis of anomalous muscle bundle has been made according to the criteria of Fellows et al.[9] The obstruction to pulmonary blood flow is determined not only by the actual amount of muscular hypertrophy, but perhaps by the position of the anomalous muscle bundle.[11]

Angiographically, the anomalous muscle bundle takes the form of 1 or more radiolucent bands crossing the right ventricular cavity with a diagonal orientation at a higher or lower level. In its most severe forms, it consists of a pyramidal filling defect with the base broadly attached to the anterior free wall of the right ventricle and with the apex protruding superiorly and posteriorly close to the septal band and the tricuspid ring[9–11] (Fig. 1).

Hypertrophy of os infundibular muscle bundles with stenosis of the os infundibulum may produce right ventricular outflow tract obstruction. Isolated stenosis at this level can be differentiated from classic tetralogy of Fallot.[9] Angiographically, this form of obstruction takes the form of a discrete narrowing of the proximal infundibulum (Fig. 2).

Tetralogy of Fallot: The morphologic (and angiographic) essence of tetralogy of Fallot is anterosuperior deviation or malalignment of the infundibular septum from the limbs of the trabecula septomarginalis.[12–14] This cephalad deviation results in actual or potential subpulmonary muscular obstruction with the ventricular septal defect below the malaligned septum. When the obstruction is low infundibular the length of the infundibulum is generally normal and its width is normal above the obstruction or only minimally decreased. When both the infundibular septum and the anterior infundibular wall are also hypertrophied, the infundibulum is often diffusely narrowed.[12]

The angiographic recognition of a malaligned infundibular septum has been made according to the criteria of Bargeron et al.[14] It is known that some patients will exhibit right ventricular outflow tract obstruction resulting from both a malaligned infundibular septum and anomalous muscle bundle. In these cases, the mid- or the apical portion of the trabecular septomarginalis are usually hypertrophied.[15]

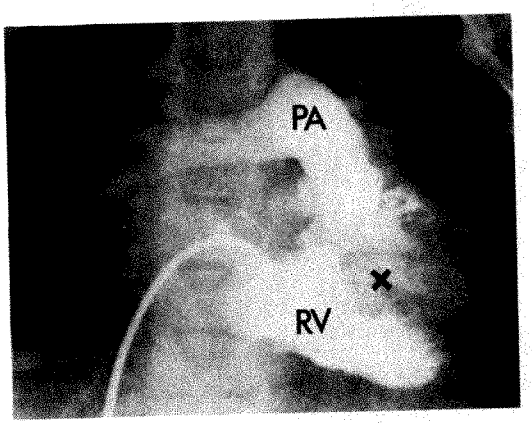

FIGURE 1. Anomalous right ventricular muscle bundles. Frontal right ventriculogram demonstrates an abnormal muscular bar (X), which is pyramidally shaped and divides the inlet from the outlet or infundibular zone of the morphologic right ventricle (RV). PA = pulmonary artery.

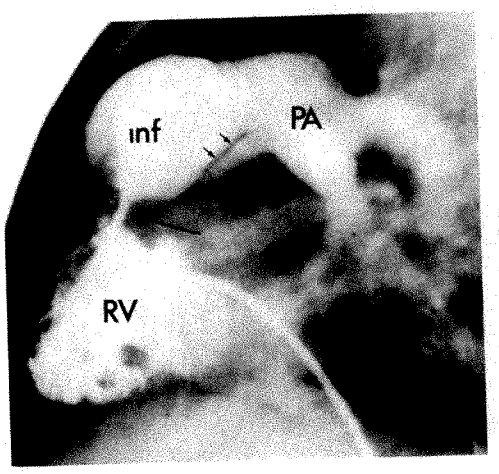

FIGURE 2. Isolated stenosis of the ostium of the right ventricular infundibulum. This lateral right ventriculogram shows a very severe concentric muscular stenosis (**large black arrow**) of the proximal infundibulum. The infundibular chamber (inf) is well demarcated. The pulmonary valve leaflets (**small black arrows**) are slightly thickened. Abbreviations as in Figure 1.

Methods

Patient selection: All hemodynamic and angiographic data were obtained from patients studied in the cardiac catheterization laboratory of the Hospital for Sick Children, Toronto, Ontario, Canada. From 1970 through 1981, we identified 20 patients with ventricular septal defect in whom right ventricular outflow tract obstruction was acquired. Their angiocardiographic findings form the basis for this report. During the same interval, about 2,541 patients with isolated ventricular septal defect were assessed clinically at this institution. All patients had levocardia, atrial situs solitus, and a "right-handed" ventricular loop with atrioventricular and ventriculoatrial concordance. Criteria for inclusion in the study included a right ventricular to pulmonary artery pressure gradient of 15 mm Hg or less at the first catheterization study and a pressure gradient of 25 mm Hg or more at the subsequent investigation.

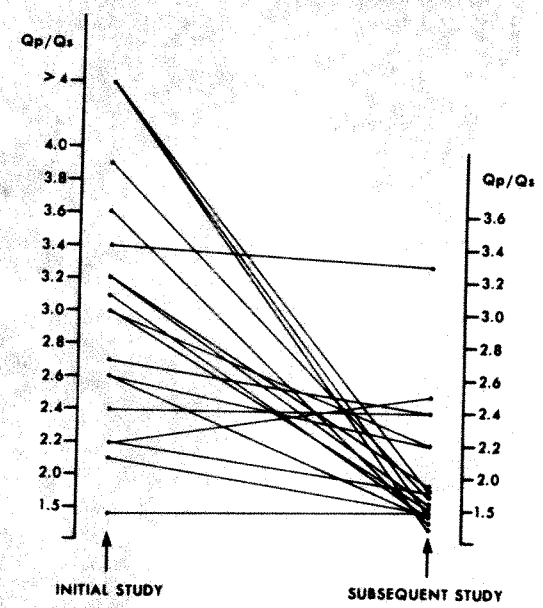

FIGURE 3. Graph depicting the change in pulmonary to systemic blood flow ratio (QP/QS) from the initial catheterization study to the subsequent study.

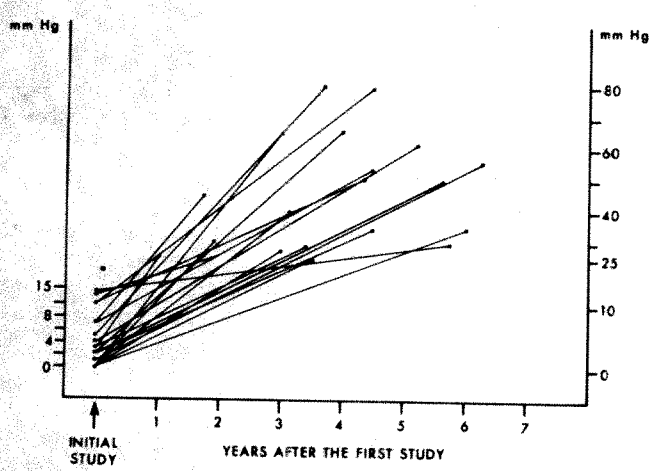

FIGURE 4. Graph demonstrating the acquisition of right ventricular outflow tract obstruction over the same time course as in Figure 3. The **vertical axes** indicate the maximal systolic pressure gradient between the right ventricle and pulmonary artery.

Angiocardiography: All patients had left ventricular angiograms performed in either the left anterior oblique or elongated axial views as advocated by Bargeron et al.[16] at the first catheter study; the left ventricle was approached either through a foramen ovale defect or retrograde from the femoral artery. Two patients had right ventricular angiograms at the initial study. At the second catheter study all patients had frontal and lateral biplane right ventricular cineangiocardiograms, and biplane left ventriculograms were again performed in all patients using the left and right anterior oblique or the elongated axial projections.

Hemodynamics: Complete hemodynamic data were obtained in all patients before angiography. Pulmonary to systemic flow ratios were calculated using either oximetry data or forward dye curves. All pressure data were obtained using fluid-filled catheters interfaced with a Hewlett-Packard 889A system.

Results

Twenty patients were identified from 1970 to 1981 who satisfied the criteria of acquiring a right ventricular outflow tract gradient of 25 mm Hg or more. There were 15 boys and 5 girls. The age at the initial catheterization study ranged from 4 days to 23 months (median 3 months, mean 4.4 months + 5.3 [standard deviation]), and at the second study from 13 months to 8 years (median 4.54 months, mean 4.34 ± 1.64). The time elapsed between the 2 investigations was 3 years 10 months ± 1 year 6 months.

Hemodynamics: Systemic arterial oxygen saturation was normal in each patient at the initial investigation. The pulmonary to systemic flow ratio ranged from 1.4:1 to 7.5:1 (median 3.05:1, mean 3.12 ± 1.3). At the second investigation, only 15 percent of patients had evidence of systemic arterial desaturation (less than 95%), and in these patients the oxygen saturation ranged from 92 to 94%. In the remainder of the patients arterial blood saturation was normal at the second investigation. The pulmonary to systemic flow ratio at this study ranged from 1.2 to 3.4 (mean of 1.8 ± 0.5, median 1.75) (Fig. 3).

All patients had a right ventricular outflow tract pressure gradient at the initial catheter study of 15 mm Hg or less (despite large shunts). The right ventricular outflow tract pressure gradients ranged from 0 to 14 mm Hg (mean 4.15 ± 4.5, median 2.4), with 17 of the 20 patients having an initial right ventricular to pulmonary artery gradient of less than 10 mm Hg. The second investigation revealed that the right ventricular outflow tract obstruction gradients had increased, ranging from 25 to 80 mm Hg (mean 45.6 ± 18.1, median 42.5) (Fig. 4). The pressure in the right ventricle ranged from 20 to 75 mm Hg at the first catheterization (median 47.5; mean 53.6 ± 14.0) and from 46 to 110 mm Hg (median 78, mean 70.1 ± 30.7) at the following study.

Left ventricular angiography: The ventricular septal defect was perimembranous in all, but extended to and was confluent with an infundibular or subarterial ventricular septal defect in 4 patients or extended posteriorly and involved the muscular inlet septum in 12 patients. One patient had multiple ventricular septal defects (perimembranous and small muscular trabecular ventricular septal defects). No patient had swiss-cheese defects. A so-called aneurysm of the perimembranous ventricular septum was not identified in any patient at the initial investigation, and at the subsequent study 3 aneurysms were demonstrated (15%). The gradient across the right ventricular outflow tract in these patients ranged from 0 to 7 mm Hg at the first study and from 27 to 50 at the second one. No patient showed hemodynamic or angiocardiographic evidence of left ventricular outflow tract obstruction during the course of this study.

Right aortic arch was identified in 3 patients (15%). Their gradient across the right ventricular outflow tract was 3 to 7 mm Hg at the first study and 29 to 62 mm Hg at the subsequent one.

Right ventricular angiography: We identified angiographically only 2 mechanisms responsible for

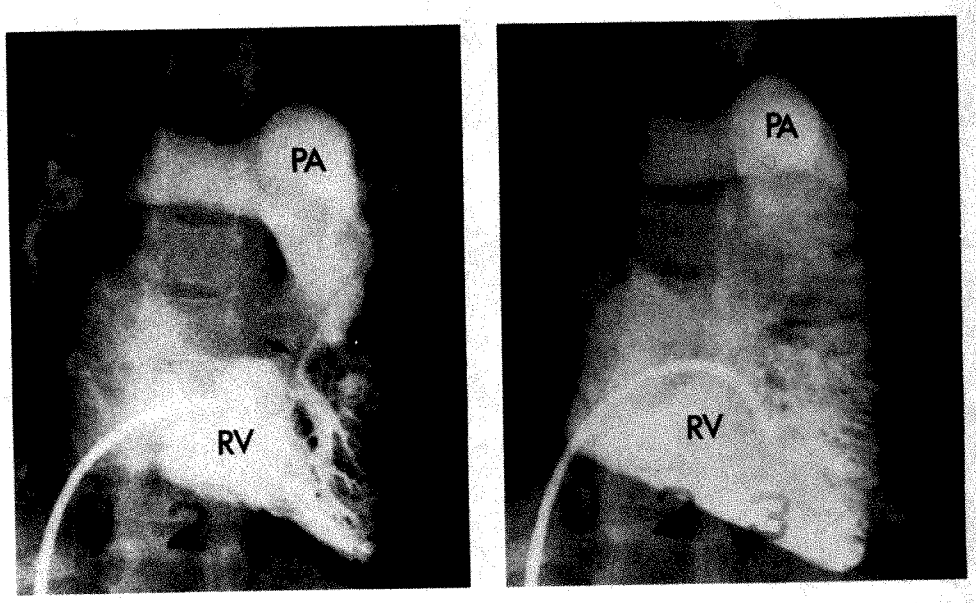

FIGURE 5. Angiographic appearance of hypertrophied right ventricular muscle bundles (**arrow**) in systole (**left**) and diastole (**right**). Abbreviations as in Figure 1.

acquired right ventricular outflow tract obstruction in the setting of isolated ventricular septal defect. Among the 20 patients included in this study, the morphologic basis for acquired right ventricular outflow tract obstruction was identified as being secondary to hypertrophy of right ventricular anomalous muscle bundles in 19. As noted earlier, right ventriculograms were performed in only 2 patients at the initial investigation because their pressure gradient across the right ventricular outflow tract was small and was attributed to the high pulmonary blood flow. Thus, we are unable to state with certainty whether right ventricular muscle bundles (amomalous or not) were present at the initial study, and that their hypertrophy over time led to subsequent right ventricular outflow tract obstruction. Conversely, the other explanation is de noveau development and hypertrophy of anomalous muscle bundles as the cause of the obstruction. We think that a malaligned infundibular septum is, of course, congenital in origin, but that its hypertrophy resulted in the evolution of the obstructive phenomenon.

Anomalous muscle bundles are easily demonstrated during ventricular systole but are less conspicuous during diastole[10] (*Fig. 5*). There is considerable heterogeneity among the angiographic appearances of right ventricular muscle bundles, and our patients exhibited the entire spectrum. In some patients the obstruction appeared primarily in the os infundibulum (but without malalignment of the infundibular septum), while in others there was a classic appearance of a hypertrophied or possibly misplaced moderator band clearly separating the inlet of the right ventricle from the outlet zone. Many patients exhibited combinations of both features with extensive hypertrophy of the apical trabecular zones as well. Only 1 patient was identified as showing the classically malaligned infundibular septum consistent with the classic tetralogy of Fallot. This patient also demonstrated heavy septal trabeculation, but this is considered typical of the usual type of tetralogy of Fallot.

No patient exhibited pulmonary valvular stenosis as the primary cause of acquired right ventricular outflow tract obstruction. Five patients, however, did show evidence of a somewhat thickened pulmonary valve at the second catheterization.

Aortic valve deformities: Aortography was performed in 11 patients at the initial study, and at the subsequent investigation 16 patients underwent retrograde aortography. We were surprised to find that 10 patients demonstrated aortic valve prolapse to a mild or moderate degree. Prolapse of the noncoronary cusp occurred in 1 patient; 5 patients had prolapse of the right cusp, 1 of the left, and 3 of the right and posterior cusps. The prolapsing cusp(s) resulted in mild aortic valve regurgitation in 4 patients.

Surgical correlates: Thirteen of these 20 patients have undergone open heart surgery, with closure of the ventricular septal defect in all cases and repair of right ventricular outflow tract obstruction. In each patient the angiographic type of right ventricular outflow tract obstruction was confirmed.

Discussion

Mechanisms of acquired right ventricular outflow tract obstruction: Several morphologic mechanisms can lead to acquired right ventricular outflow tract obstruction in patients with an isolated ventricular septal defect. They include, singly or in combination: (1) hypertrophy of malaligned infundibulum (so-called tetralogy-type); (2) anomalous right ventricular muscle bundles; (3) so-called wind-sock aneurysm of membranous septum[17]; (4) development of a subpulmonary fibrous diaphragm[18,19]; (5) accessory tricuspid leaflet[20]; (6) neoplasm[21]; and (7) other.[22] Numerous case reports have identified the mechanism responsible for acquired right ventricular outflow tract obstruction in 1 or a few patients. However, it is unclear what mechanisms are most frequently responsible for acquired right ventricular outflow tract obstruction in any cohort of patients studied in a single institution. One could assume

that either a tetralogy-type of right ventricular outflow tract obstruction or anomalous muscle bundles should be the most prevalent mechanism. Rather, the focus of attention of the "natural history" studies is on the incidence of this phenomenon rather than the mechanism. Previous reports frequently refer to acquired right ventricular outflow tract obstruction as a "tetralogy-like" phenomenon, and one could not dispute this in terms of the hemodynamic evolution. However, our data strongly support the view that acquired right ventricular outflow tract obstruction in patients with an isolated ventricular septal defect is rarely of the classic tetralogy-type. Rather, the obstruction seems to result from hypertrophy of right ventricular muscle bundles, whether anomalous or not. Although in our series 1 of 20 patients (5%) had right ventricular outflow tract obstruction due to infundibular malalignment, could our data, because of a small patient population, have underestimated its true frequency? Statistical analysis using the standard binomial formula[23] suggests that our results would be improbable ($p = 0.025$) if malalignment caused more than 25% of cases and unlikely ($p = 0.1$) if it caused more than 17.5% of cases.

Varghese et al.[6] reviewed the natural history of 14 patients with ventricular septal defect and right aortic arch with particular emphasis on the incidence of and mechanisms responsible for acquired right ventricular outflow tract obstruction. Their data suggest that in 6 patients anomalous muscle bundles seemed responsible for the acquisition of right ventricular outflow tract obstruction, whereas in 2, the obstruction was of a more classic tetralogy type. Two other cases presented unclear characteristics.

Right ventricular anatomic considerations: Considerable attention has previously been focused on the disposition of muscle bundles in the apical trabecular and infundibular zones of the normal as well as the abnormal right ventricle. What is unclear from our data is whether right ventricular outflow tract obstruction can be acquired in the presence of a "normal" right ventricular myocardial matrix, or whether even in the absence of a pressure gradient, right ventricular myocardial abnormalities may be present which have the late potential for hypertrophy and obstruction. In this regard, we presented elsewhere[24] persuasive angiographic evidence that fatal subaortic stenosis can develop rapidly in an infant previously shown to have an angiographically normal left ventricular outflow tract.

Among our 20 patients, 2 had right ventricular cineangiocardiograms at the initial catheter investigation, and 1 of these was considered entirely normal. The second one presented an enlarged right ventricle and features of transient myocardial ischemia. We were not impressed with the angiographic appearance of the disposition of right ventricular muscle bundles, or the potential for evolution into obstruction. Furthermore, although Tyrrell et al.[25] and others[9] have commented on the horizontal geometry of the pulmonary artery as a harbinger of acquired right ventricular outflow tract obstruction in patients with ventricular septal defect, this finding was absent in our group of patients.

Acquired subaortic stenosis was not found in this particular group of patients, although like Baumstark et al.[26] we have also observed this occurrence in patients with ventricular septal defect and right ventricular anomalous muscle bundles. We were surprised by the high incidence of aortic valve deformities in our group of patients, most of whom did not have infundibular subarterial ventricular septal defects.

We conclude that in patients with isolated ventricular septal defect acquired right ventricular outflow tract obstruction usually results from hypertrophy of anomalous muscle bundles.

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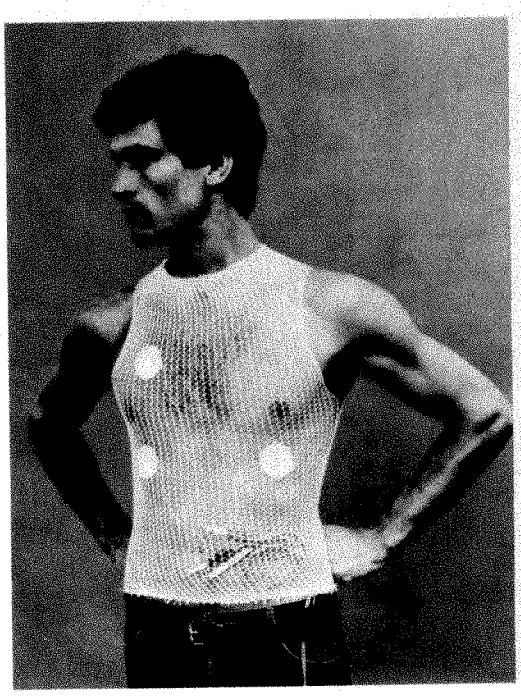

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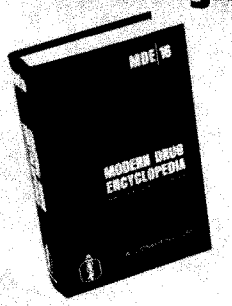

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Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported, as have fever, respiratory difficulty, thrombocytopenia, and gynecomastia. **Dosage and Administration:** Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses. The recommended dosage schedule for most adults is either 150 mg every six hours for immediate-release Norpace or 300 mg every 12 hours for Norpace CR. For patients less than 110 pounds (50 kg) the recommended dosage is either 100 mg every six hours for immediate-release Norpace or 200 mg every 12 hours for Norpace CR. If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients less than 110 pounds) is recommended. 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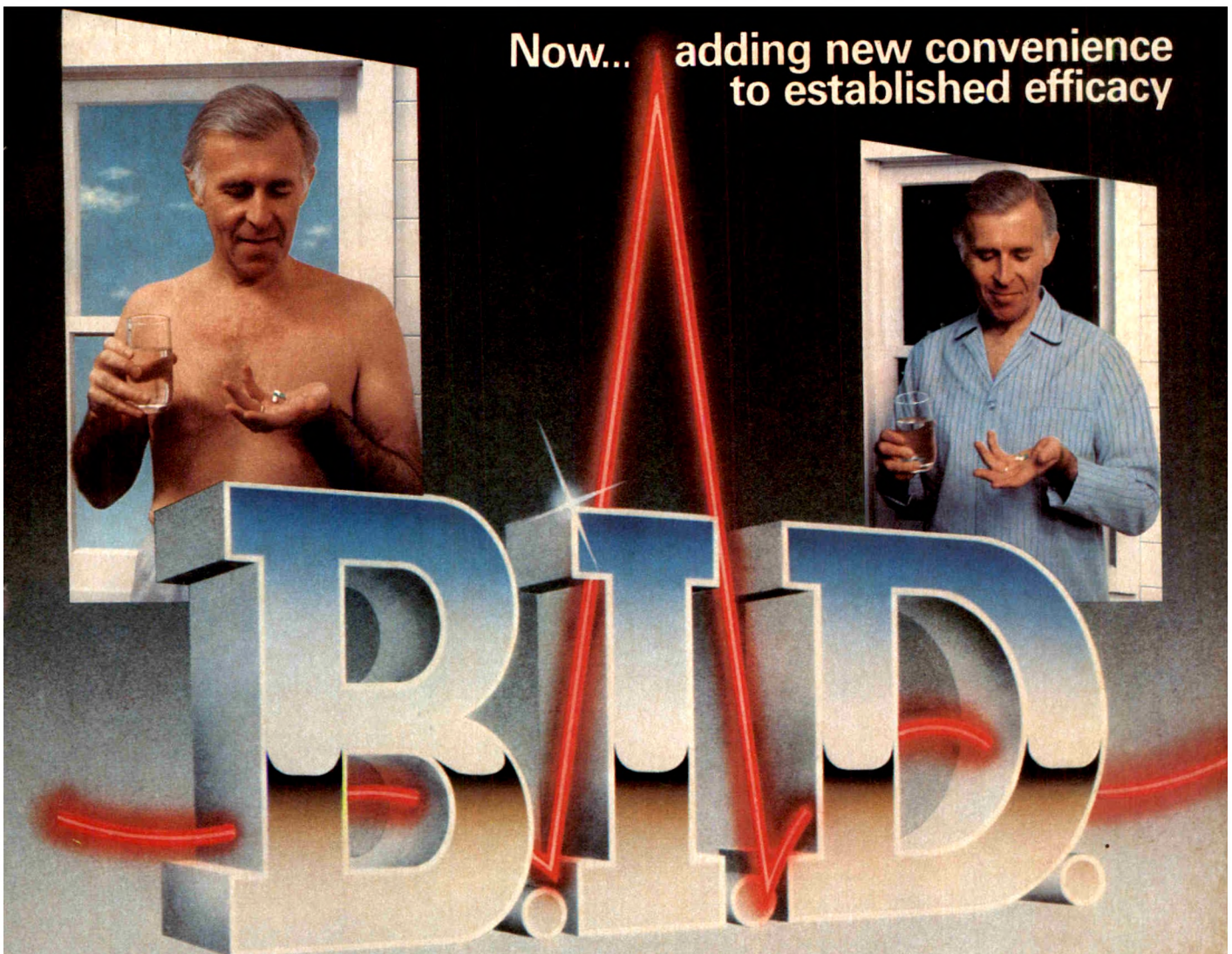

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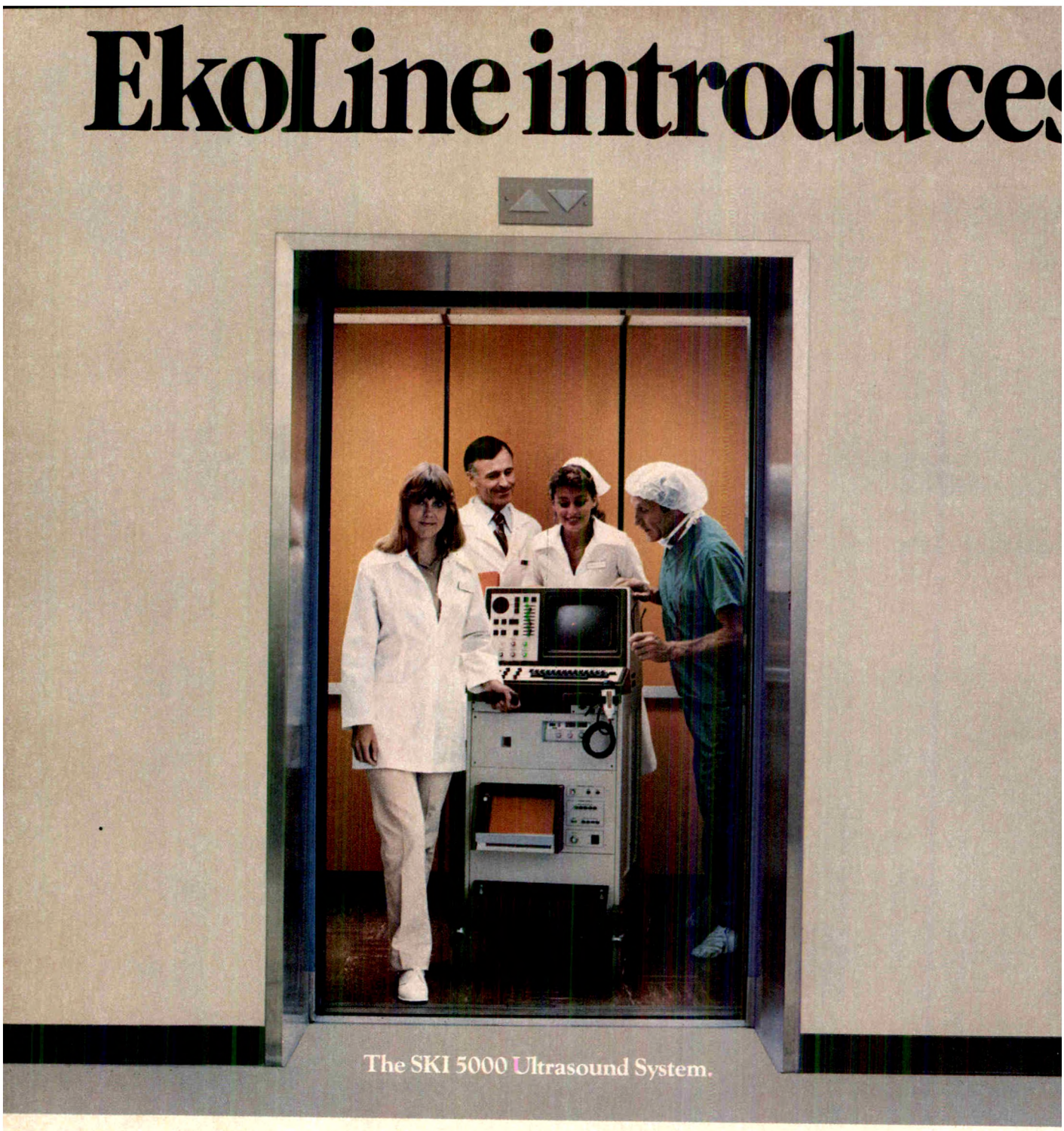

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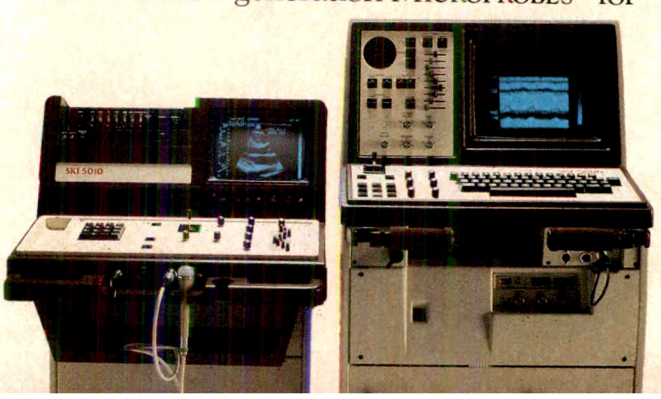

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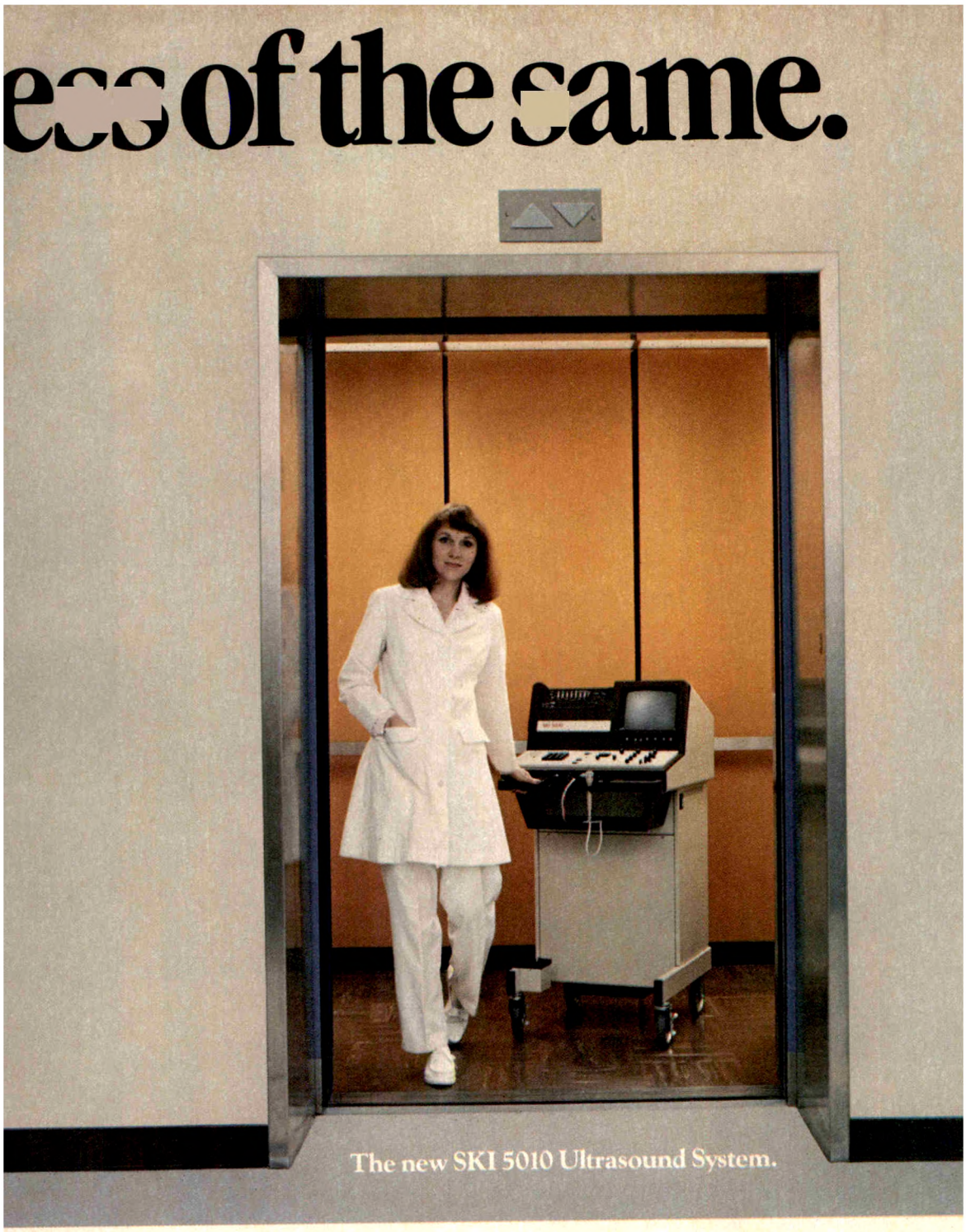

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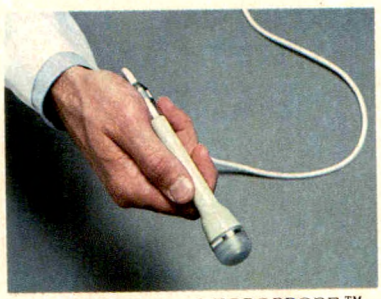

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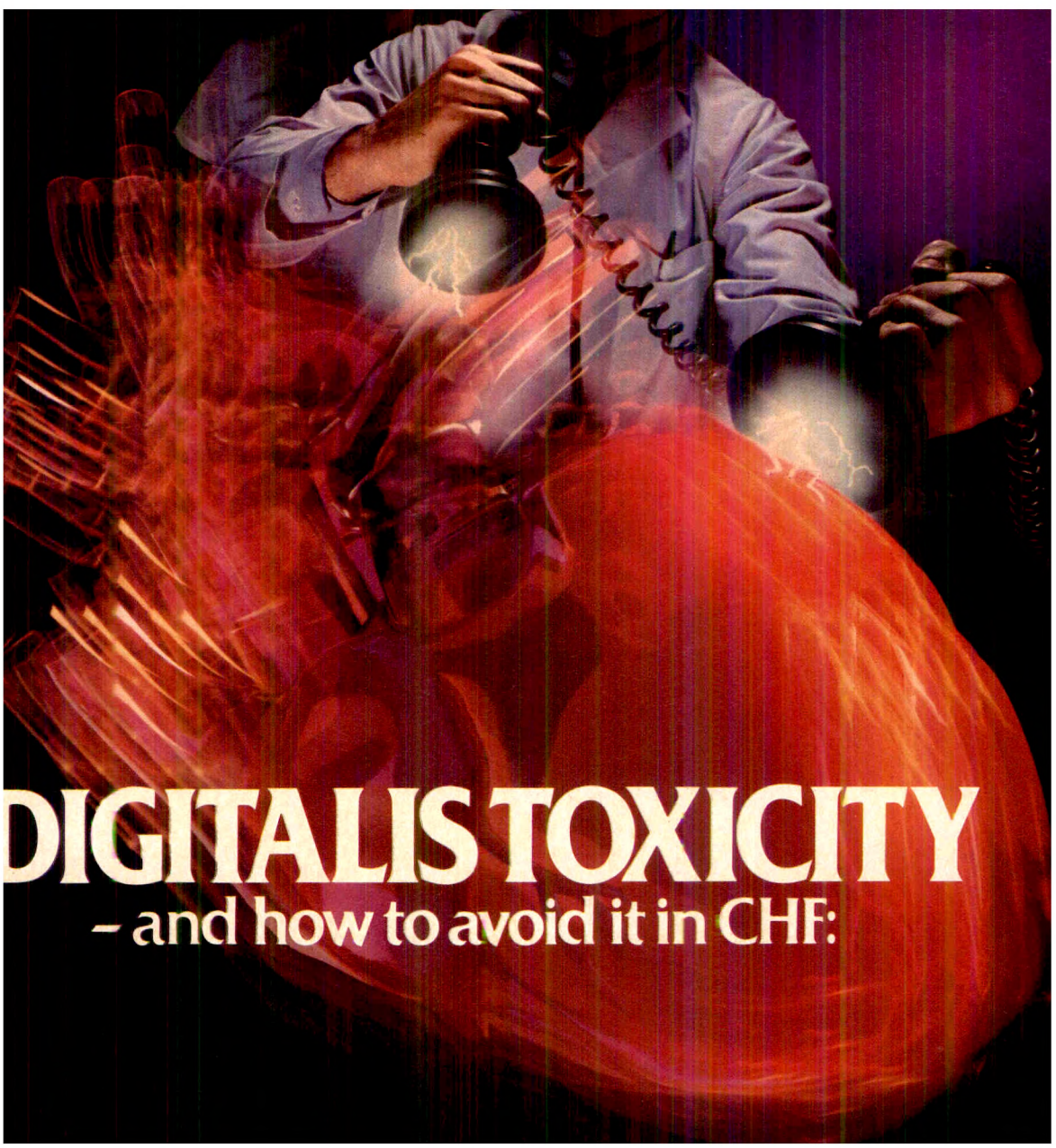
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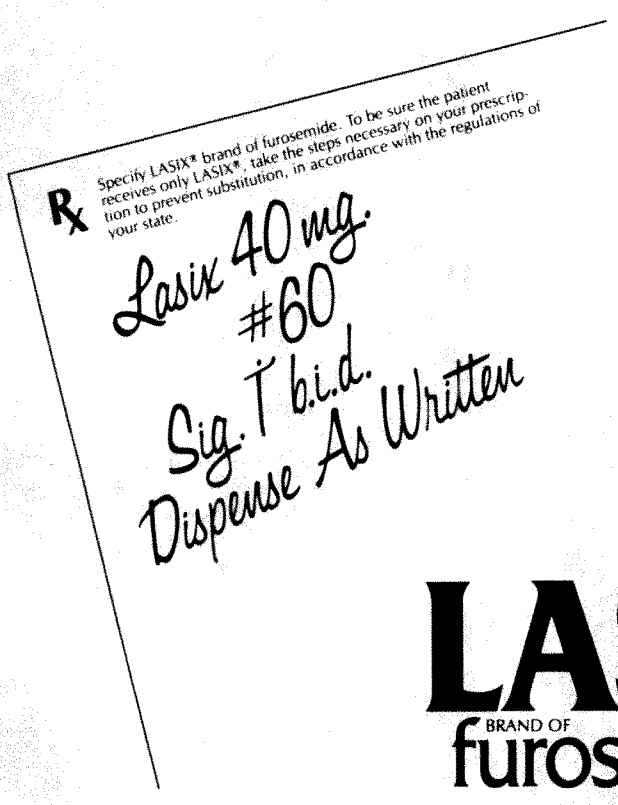

If you are in doubt about a particular generic furosemide, call the offices of the Food and Drug Administration's Bureau of Drugs, Consumer and Professional Relations staff at 301-443-1016.

Reference: 1. Koch H: Drugs most frequently used in office-based practice: National Ambulatory Medical Care Survey, 1980, Vital and Health Statistics of the Nat Ctr for Health Statistics, No. 78 (May 12) 1982.

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Lasix® (furosemide)

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WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

PREGNANCY: Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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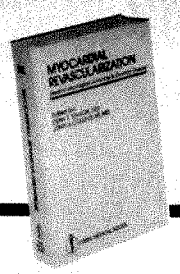

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Surgical Repair of Congenitally Corrected Transposition of The Great Arteries: Results and Follow-Up

BETAU HWANG, MD, FREDERICK BOWMAN, MD, JAMES MALM, MD, and EHUD KRONGRAD, MD

Eighteen patients with congenitally corrected transposition of the great arteries had open heart repair for intracardiac associated defects. Fourteen patients (78%) are alive during the follow-up period (mean 4.5 years). Seventeen (94%) of the 18 patients had ventricular septal defect closure, and 12 (66%) insertion of a pulmonary artery conduit. Surgical repair of the tricuspid valve was required in 6 patients (33%) during the first operation and in 3 additional patients during a second operation (total 50%). When hemodynamic overload or cardiac compromise was detected after surgery it was directly related to identifiable residual defects such as atrioventricular valvular insufficiency, residual ventricular septal defect, or pulmonary conduit stenosis. Repeat open heart operation for residual defects was common during the follow-up period (8 of 18 patients, 44%). No patient showed primary systemic or pulmonary ventricular dysfunction during the follow-up period. None of the last 11 patients developed complete heart block. Postoperative intraventricular conduction defects were common and are presumably caused by surgical injury of the bundle branches.

Our observations suggest that surgical repair of congenitally corrected transposition of the great arteries can be currently achieved with acceptable risk. Improved knowledge of the precise location of the specialized conduction system resulted in a marked decrease in the incidence of atrioventricular (A-V) block in patients with congenitally corrected transposition of the great arteries undergoing intracardiac repair. In the absence of postoperative residual defects it can be expected that longevity and quality of life will improve considerably, but many of these patients may require a repeat operation.

Congenitally corrected transposition of the great arteries is an uncommon congenital malformation of the heart. It is a congenital malformation with arterioventricular discordance in which the anatomic right ventricle is usually on the side opposite that occupied by the liver and the aorta emerges from the anatomic right ventricle and is placed anterior and usually leftward to the pulmonary artery. Surgical experience with congenitally corrected transposition of the great arteries to this date has been limited. Complete surgical repair is usually associated with high mortality, high morbidity, and a high incidence of surgically induced complete heart block.[1-3] In general, early and late results were less favorable when compared with outcome achieved after repair of other congenital cardiac malformations. Further, concern has been raised regarding the postsurgical status of the left-sided (anatomic right) ventricle and its tricuspid valve and their long-term ability to function well under systemic pressure.[2] This report presents our experience and the outcome of open heart repair in patients with congenitally corrected transposition of the great arteries.

From the Department of Pediatrics, Pediatric Cardiology, Babies Hospital and the Surgical Service of Presbyterian Hospital and the College of Physicians and Surgeons, Columbia University, New York, New York. Manuscript received January 26, 1982; revised manuscript received February 12, 1982, accepted April 16, 1982.

Address for reprints: Ehud Krongrad, MD, Department of Pediatrics, Babies Hospital, 3959 Broadway, New York, New York 10032.

Methods

Patient population: During the years 1969 to 1980, 41 patients at Columbia-Presbyterian Medical Center had various forms of open or closed surgical treatment for congenitally corrected transposition of the great arteries with 2 ventricular

chambers. Eighteen of the 41 had open heart repair and are the subject of this report, and 23 additional patients had various closed procedures. The patients' age at the time of open heart surgery ranged from 6 to 38 years (median 13). Fourteen patients were male and 4 were female. A total of 26 open heart procedures were carried out in these 18 patients. Fourteen (78%) of the 18 patients are alive, and their follow-up period ranged from 11 months to 10.5 years (median 4.5).

Various types of open heart procedures utilized to repair the intracardiac defects (Table I): Eight patients had ventricular septal defect closure and insertion of a pulmonary artery valved conduit. Four patients had closure of a ventricular septal defect and left side atrioventricular (A-V) valve repair during the first open heart operation. Three of these 4 patients required valve replacement and in 1 patient tricuspid (left A-V valve) valvuloplasty was carried out. Three patients required plication of a membranous septal aneurysm including closure of a ventricular septal defect.[4] Two of these 3 patients required in addition a pulmonary valved conduit, and 1 patient required pulmonary infundibulectomy. One patient had closure of a ventricular septal defect, insertion of a pulmonary artery valved conduit, and left A-V valve replacement. Two additional patients had open heart surgery. The first had left-sided A-V valve replacement alone and the other had ventricular septal defect closure, placement of a pulmonary artery valved conduit, and right-sided A-V valve replacement. Thus, 17 of the 18 patients had ventricular septal defect closure, 12 had insertion of a pulmonary valve conduit and 6 had left sided A-V valve repair or replacement during the first open heart procedure.

Additional open heart surgery was subsequently carried out in 8 patients (Table II). Two patients required closure of a residual ventricular septal defect; 2 patients subsequently had left-sided A-V valve replacement. One patient had left sided A-V valve anuloplasty and an additional patient had right sided A-V valve anuloplasty. Two patients required replacement of a stenotic pulmonary ventricle to pulmonary artery valved conduit.

Mapping of atrioventricular conduction: Intracardiac mapping for delineation of the His bundle was carried out in 11 of the 18 patients (Table III). After intracardiac mapping 2 of the 11 patients developed transient prolongation of the P-R interval on the electrocardiogram, and there was no change in A-V conduction in the other 9 patients. During this time open heart repair was carried out in 7 additional patients without the aid of intracardiac mapping. Of the 7 patients without intracardiac mapping 1 developed prolonged P-R interval, 2 patients developed permanent complete A-V block, and 1 patient developed transient complete A-V block.

TABLE I Surgical Procedures Employed During First Open Heart Repair in 18 Patients With Congenitally Corrected Transposition of the Great Arteries

VSD closure + PA valved conduit	8
VSD closure + left A-V valve repair	4
Plication of membranous septal aneurysm	3
VSD closure + PA conduit + left A-V valve replacement	1
VSD closure + PA valved conduit + right A-V valve replacement	1
Total	18

A-V = atrioventricular; PA = pulmonary artery; VSD = ventricular septal defect.

TABLE II Additional Open Heart Operations Required Subsequently in the Same Patient Population

	n
Residual VSD	2
Left A-V valve replacement	2
Left A-V valve anuloplasty	1
Right A-V valve anuloplasty	1
LV-PA conduit replacement	1
Total	7

LV = left ventricular; other abbreviations as in Table I.

TABLE III Effect of Intracardiac Mapping on Subsequent Development of Complete Heart Block

	A-V Conduction Defects			
Procedures	1°	2°	3°	No Change
No mapping (7 patients)	1	0	3*	3
Mapping (11 patients)	2	0	0	9

* Two cases of permanent atrioventricular (A-V) block and 1 of transient complete A-V block.

Results

Mortality: Four (22%) of the 18 patients died. Two patients died early after reoperation for residual ventricular septal defects. One of these 2 patients had a small systemic (right) ventricle which most likely contributed to the poor outcome. One patient died 3 months after surgery from hepatitis and 1 patient died suddenly, presumably from cardiac arrhythmia. The latter patient was known to have complete heart block, an artificial pacemaker, and recurrent premature ventricular contractions.

Follow-up: Three patients who were clinically well and did not require subsequent repeat open heart surgery had a postsurgical cardiac catheterization. All showed normal systemic saturation, none had an intracardiac right-to-left or left-to-right shunt. All had trivial residual pulmonary stenosis of 10 to 12 mm Hg; all 3 showed good systemic right ventricular function. Systemic ventricular function was also determined during cardiac catheterization in 6 additional patients who required repeat operations for various residual defects. In 5 of these patients the systemic ventricular function was considered good by hemodynamic and angiographic techniques, and in 1 patient with severe tricuspid incompetence systemic ventricular function was considered poor.

Conduction defects: Intraventricular conduction defect with QRS prolongation and secondary ST-T wave changes were often noted immediately after open heart surgery. In the late postoperative period, 10 patients showed an intraventricular conduction defect with QRS prolongation and ST-T wave changes and 2 patients who are doing well show minimal ST-T wave changes without QRS prolongation (Fig. 1).

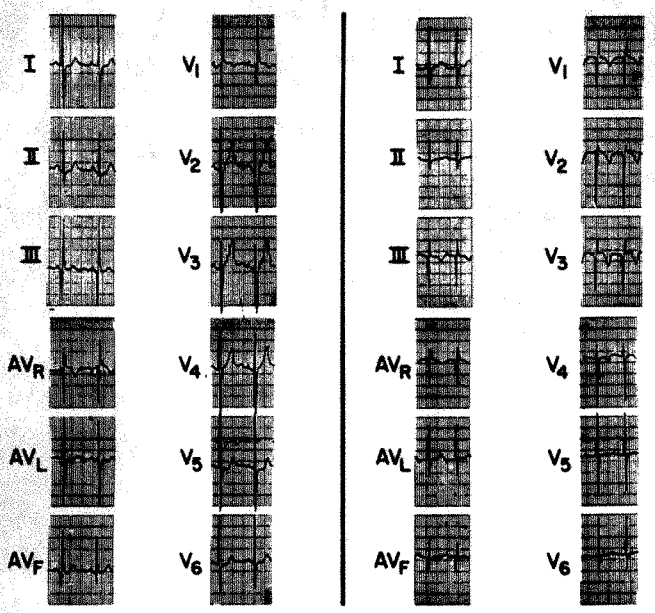

FIGURE 1. Preoperative (**left**) and postoperative (**right**) electrocardiograms in a patient with congenitally corrected transposition of the great arteries who had closure of a ventricular septal defect and insertion of a left ventricular to pulmonary artery conduit. Note that the QRS duration of 0.06 second is similar in the pre- and postoperative tracings in spite of a large left ventriculotomy. The postoperative tracing shows prolongation of the P-R interval to 0.20 second. This patient was 1 of 2 patients who had intraoperative mapping and a residual postoperative A-V conduction disturbance.

Discussion

Indications and results of corrective surgery: Hemodynamically significant cardiac lesions are present in almost all patients with congenitally corrected transposition of the great arteries.[5–10] It is estimated that for such patients the median age of death is 8 years and 3 months and that only 30% of patients get to be 10 years old.[5,10] This sharply curtailed life expectancy and significant morbidity in the form of congestive heart failure or cyanosis in almost all patients with congenitally corrected transposition of the great arteries provide the indication for repair of this uncommon and complex malformation.

In the current series 78% of the 18 patients are alive and well after surgery, with a median follow-up period of 4.5 years. These results suggest that open heart surgery in properly selected patients may be offered with acceptable risk. The prognosis in such patients is related to residual defects, systemic ventricular function, or presence of A-V block. In our patients, when hemodynamic overload or cardiac compromise was detected after surgery it was directly related to identifiable residual defects such as atrioventricular valvular insufficiency, residual ventricular septal defect, or pulmonary conduit stenosis. In the absence of postoperative residual defects it can be expected that longevity and quality of life will improve considerably. Eight of the 18 patients (44%) required a second operation for residual defects. Of these 8 patients, 4 (50%) required additional surgery for repair of either tricuspid (3 patients) or mitral insufficiency (1 patient).

Tricuspid insufficiency before and after surgical correction: Nine of the 18 patients (50%) required surgical treatment of the tricuspid valve during the first or subsequent open heart operation. This high incidence of tricuspid insufficiency noted in our patients is similar to previous angiographic,[7] pathologic,[5,7,11] and surgical observations[1–3] reporting a high incidence of tricuspid malformations in patients with congenitally corrected transposition of the great arteries. Our surgical and follow-up data suggest that the prognosis in patients with congenitally corrected transposition of the great arteries may closely be related to the integrity and function of their tricuspid valve.

It has been suggested[2] that tricuspid insufficiency tends to develop in patients with congenitally corrected transposition of the great arteries after open heart repair once the ventricular balance has been altered by closing the ventricular septal defect. It has been argued[2] that closure of the septal defect will cause the anatomic right ventricle and the tricuspid valve to face systemic pressure without a safety mechanism of tricuspid regurgitation or a ventricular defect. Our experience that 6 of 18 patients required surgical repair of the tricuspid valve during the first operation as well as previous angiographic,[7] pathologic,[5] and surgical[1–3] data indicate that primary and hemodynamically significant A-V regurgitation is common in patients with congenitally corrected transposition of the great arteries whether the ventricular septal defect is repaired or not.

Conduction defects: role of intracardiac mapping: Among our patients none of the 11 who had intracardiac mapping developed permanent complete heart block while minor transient injury to A-V conduction occurred in 2 patients. Of the 7 patients who did not have intracardiac mapping, 2 had permanent complete heart block.

The precise location of A-V conduction in congenitally corrected transposition of the great arteries differs from that in patients with atrioventricular concordance. In almost all patients with congenitally corrected transposition of the great arteries the A-V node is located anteriorly with the His bundle penetrating into the pulmonary ventricle to the right of the pulmonary artery. When a ventricular septal defect is present the His bundle bifurcates along the anterior margin of the ventricular septal defect into the left and right bundle branches. The left bundle branch continues downward along the anterior margin of the ventricular septal defect, and the right bundle branch penetrates the systemic ventricle at the superior margin of the ventricular septal defect or departs from the left bundle somewhere along the anterior margin of the ventricular septal defect. This precise localization and different location of the A-V conduction system was established in recent years by both histologic and electrophysiologic mapping techniques.[12–15]

Most of our patients who did not benefit from intraoperative mapping were operated on before the estab-

lishment of intracardiac mapping and before more recent knowledge of the different location of the conduction system in this cardiac anomaly. In this group of patients the high incidence of permanent complete heart block is similar to previously reported data.[1-3] No patient who had the benefit of intracardiac mapping developed permanent complete heart block. In each of these patients the precise and different location of the A-V conduction system was identified.

The increased knowledge regarding the expected anatomic location made the mapping procedure increasingly brief. With the current knowledge of the precise and different location of A-V conduction in congenitally corrected transposition it is doubtful that electrophysiologic mapping will produce in the future such a substantial difference in the preservation of A-V conduction as seen in our series. However, during the early years when the precise location of A-V conduction was not firmly established this method was definitely helpful in avoiding injury to the A-V conduction system. Our data in these patients indicate that electrophysiologic mapping should be used in any patient in whom the precise location of the conduction system is in doubt.

Intraventricular conduction defect in the form of right bundle branch block pattern is common after open heart surgery for repair of ventricular septal defect or associated pulmonary stenosis, or both.[16,17] This may result from a right ventriculotomy, surgical injury to the right bundle branch, or myocardial damage. Most of our patients showed QRS prolongation and S-T and T-wave changes after surgery. Since poor myocardial function secondary to severe tricuspid insufficiency was detected in only 1 of our patients, it is felt that the postoperative S-T and T-wave changes result most probably from injury to the cardiac conduction system. In patients with congenitally corrected transposition of the great arteries, intraoperative injury to the intraventricular conduction system may conceivably occur during ventriculotomy (when done) or be caused by direct trauma to the right or left bundle branch, or both.[18] Complete injury to the His bundle may be avoided by precise localization of the His bundle and by placing the stitches on the left or on the right septal surfaces away from the conduction system. It has been suggested[18] that in most patients with congenitally corrected transposition of the great arteries the intraventricular conduction defects result from injury to either the left or the right bundle branch, or both, rather than from left ventriculotomy. As observed by Griffiths et al.[19] and by Castagna et al.,[18] left ventriculotomy is usually not associated with significant ventricular conduction delay. This is true whether the left ventricle is in the normal relation[19] or inverted as in congenitally corrected transposition of the great arteries.[18,20]

Optimal age for open heart surgery and preliminary staging operation: Finally, the median age of our patients at the time of open heart repair was 13 years (range 6 to 38). This is a more advanced age compared with other types of elective surgery carried out on most patients with congenital heart disease. The median age of our patients is probably affected by satisfactory palliative operations and surgical experience of early years.

The optimal age for open heart repair is dependent on the underlying associated cardiac defects. In young patients with severe pulmonary obstruction and cyanosis an aortic to pulmonary shunt, usually in the form of a Blalock-Taussig shunt, is advisable. Pulmonary artery banding is advised in very young infants with a ventricular septal defect and pulmonary hypertension without A-V valvular insufficiency.

Elective open heart repair in patients with isolated ventricular septal defect and no pulmonary stenosis should be carried out at age 4 to 6 years. Although pulmonary artery banding is advisable in young infants with pulmonary hypertension, primary ventricular septal defect repair can conceivably be offered to children younger than 4 years of age.

Repair of ventricular septal defect and pulmonary stenosis: In the current patient population, all ventricular septal defects were repaired via a ventriculotomy. However, surgical closure of the ventricular septal defect via a right atrial approach or via the pulmonary artery has been reported.[21,22] Indeed, this approach was used in a patient operated on recently.[23]

Our experience shows that most patients with a ventricular septal defect and pulmonary stenosis require insertion of a pulmonary artery conduit since resection of the subvalvular pulmonary obstruction is limited by the coronary arterial anatomy and by the likelihood of creating atrioventricular block. Patients with congenitally corrected transposition of the great arteries who require insertion of a pulmonary artery conduit should be electively operated on after 6 years of age to allow insertion of an optimal conduit size. Elective surgery should not be postponed beyond adolescence because of secondary myocardial changes associated with ventricular hypertrophy.

Implications: The results and follow-up of our patients suggest that surgical repair of congenitally corrected transposition of the great arteries can be offered with a significantly decreased risk and improved outcome. They also indicate that improved knowledge of the location of the A-V conduction system should result in a marked decrease in the incidence of surgical complete heart block. When postoperative clinical deterioration occurs in such patients it almost always is due to a residual anatomic defect and frequently it is due to an associated congenital malformation of the tricuspid valve rather than to failure of the systemic ventricle. Finally, when QRS prolongation and S-T and T-wave changes occur postoperatively they often reflect intraventricular conduction defects rather than a poor myocardial state.

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Left and Right Ventricular Adaptation to Right Ventricular Overload Before and After Surgical Repair of Tetralogy of Fallot

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On the basis of angiographic projections, left (n = 43) and right (n = 56) ventricular volume data were obtained in patients with tetralogy of Fallot before and after surgical repair. The postoperative patients were divided into 3 groups according to the degree of an additional volume load secondary to a residual ventricular septal defect or pulmonary insufficiency, or both. The decreased left ventricular ejection fraction ($p < 0.01$) in preoperative tetralogy of Fallot in the presence of a normal sized left ventricle suggests depressed global myocardial function, which is not improved after surgical repair, even if excellent results are achieved. A certain functional reserve, however, seems to be preserved, since the ejection fraction did not decrease further with increasing additional volume loads.

Similar enlargement of the right ventricle secondary to comparable degrees of pulmonary insufficiency and residual ventricular septal defect indicates similar effects of additional diastolic and systolic filling on right ventricular function in patients with tetralogy of Fallot after surgical repair. Even in patients with excellent surgical results, such as those without significant right ventricular outflow tract obstruction and additional volume load, right ventricular pump function is depressed, the ejection fraction being significantly ($p < 0.01$) lower than normal. The further decrease of global myocardial function with increasing volume load suggests a loss of functional reserve. Attempts to minimize right ventricular volume load after surgical repair seem advisable.

Only limited and controversial information concerning left and right ventricular performance after surgical repair of tetralogy of Fallot is available.[1–7] For the left ventricle normal[2] as well as decreased[1] ejection fractions were reported in patients after successful surgical repair; in this regard the age at operation may influence the results.[8]

The right ventricle is the chamber primarily involved anatomically. Applying current surgical techniques, an additional volume load to this ventricle postoperatively cannot be prevented in many instances. However, the effect of such a volume load on right ventricular myocardial function has not been assessed precisely. The main reason appears to be the inability to quantitate the degree of myocardial function with acceptable accuracy, which was achieved in the present study with a roentgen videodensitometric method.[9] The purpose of this study therefore was to determine and compare the effect of different degrees of volume load on left and right ventricular myocardial function in patients with tetralogy of Fallot after surgical repair.

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Methods

Patient Groups (Tables I and II)

Preoperative group: Tetralogy of Fallot was defined as a combination of a large ventricular septal defect with an "overriding" aorta, allowing equalization of the pressure in the 2 ventricles, and severe right ventricular outflow obstruction, causing a bidirectional interventricular shunt with a net right-to-left shunt. Although some of the patients had a patent foramen ovale, none had evidence of interatrial shunting on oximetry or cineangiography.

Eighteen preoperative patients were studied. Three of them had a poorly functioning aortopulmonary shunt (1 Blalock-Taussig in the left ventricular group and 2 Waterston-Cooley in the right ventricular group). The ventricular volumes in these children were not larger than the mean of the respective group.

Postoperative group: Included in the postoperative group of 38 patients were those without significant residual defects (no ventricular septal defect and a maximal systolic gradient between right ventricle and pulmonary artery of 30 mm Hg or less) and those with an increased quantified preload caused by a ventricular septal defect or pulmonary insufficiency, or both. All patients had right bundle branch block.

Aortopulmonary shunts were closed at surgical repair in 5 patients in the left ventricular study group (1 Blalock-Taussig in those with a volume load less than 20%; 1 Blalock-Taussig and 3 Waterston-Cooley in those with a volume load greater than 50%) and 6 patients in the right ventricular study group (1 Blalock-Taussig in those with a volume load less than 20%; 2 Blalock-Taussig in those with a volume load of 20 to 50%; 1 Blalock-Taussig and 2 Waterston-Cooley in those of a volume load greater than 50%). Infundibulectomy and closure of the ventricular septal defect with a patch as well as commissurotomy or insertion of a transanular patch, or both, were performed in all patients. A transanular patch was utilized in 18 patients in the left ventricular study group (9 transanular patches with 2 monocusps in those with a volume load less than 20%; 6 transanular patches with 2 monocusps in those with a volume load of 20 to 50%; 3 transanular patches without monocusps in those with a volume load greater than 50%) and 25 patients in the right ventricular study group (3 transanular patches without monocusps in the group with a volume load less than 20%; 10 transanular patches with 2 monocusps in those with a volume load of 20 to 50%; 12 transanular patches with 5 monocusps in those with a volume load greater than 50%).

Angiograms: Included for study were only those patients whose angiocardiograms were of high quality, allowing a distinct border definition of the selected beat. Of the available angiocardiograms, 48% of the left ventricular angiograms and 47% of the right ventricular angiograms in the preoperative group and 70 and 58%, respectively, in the postoperative group could be analyzed. Patient age, height, weight, and body surface area for the included pre- and postoperative patients at the time heart catheterization was performed are summarized in Tables I and II. For the time from operation to restudy see Figures 7 and 8.

Study period: The study included patients studied from February 1975 to February 1980. Premedication, catheterization procedure, and quantitative analysis of routine angiocardiograms were the same during this period. Corrective surgery was performed between February 1975 and February 1979. All patients were operated on under moderate hypothermia (25 to 30°C), and hemodilution to a hematocrit of 30%. Cardioplegia has been used since 1978 in 10 patients; 7 of these children were included in the left ventricular study group (volume load less than 20%, n = 4; 20 to 50%, n = 2; greater than 50%, n = 1) and 9 in the right ventricular study group (volume load less than 20%, n = 1; 20 to 50%, n = 2; greater than 50%, n = 6).

Data Acquisition

Cardiac catheterization: The patients were studied in the fasting state in the supine position. Infants up to 12 months of age received Luminal® (acidum phenylbarbituricum) (10 mg/kg), and older children Dolantin® (pethidine) (1 to 1.5 mg/kg), Luminal® (10 mg/kg), and atropin (0.01 to 0.015 mg/kg) premedication, given 1 hour before the diagnostic cardiac catheterization.

Before the first cineangiocardiogram was taken, the shunts were quantified by oximetry. Left and right ventricular pressure was recorded using a side hole catheter (NIH 6F or 7F) connected to a Statham P23db transducer (Statham Instruments, Oxnard, California). Zero pressure was referenced to the level of the venae cavae in the lateral projection.

Angiocardiography: ventricular volumes: Volumes of the left and right ventricles were obtained on the basis of biplane videoangiocardiographic projections (anteroposterior and lateral), recorded side by side at 50 frames/s on magnetic tape together with physiologic reference data such as electrocardiogram and pressure after selective injection of 76% Urografin® (Schering AG, Berlin) into the left (1 ml/kg of body weight) or right ventricle (1.5 ml/kg of body weight). For calibration purposes a steel sphere of known diameter was filmed at the location the ventricles occupied. The borders of the biplane projections (steel sphere and ventricles in sinus beats) and "anatomic landmarks" [10] were marked with an x/y coder. Volumes at end-diastole and end-systole were calculated for the left and right ventricles with area-length and multiple slices methods, respectively.[11] All values were corrected with factors appropriate for spatial position and cardiac phase.[12,13]

The following variables for the left and right ventricle were calculated from end-diastolic and end-systolic volumes and compared with normal values, reported before[12,13]: stroke volume (end-diastolic − end-systolic volume), ejection fraction (stroke volume/end-diastolic volume), and systolic output (stroke volume × heart rate).

End-diastolic, end-systolic, and stroke volumes were normalized for the corresponding body surface area to the power of 1.219, since we found a nonlinear relationship with an exponent of e = 1.219 between volume variables and body surface area.[12,13] The stroke output index equals stroke output divided by body surface area. Detailed descriptions of the videometric system were reported previously.[10,14]

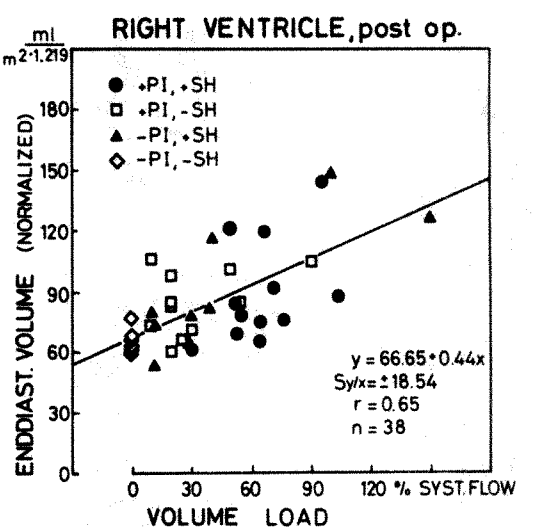

FIGURE 1. Right ventricular end-diastolic (END DIAST.) volumes (normalized for body surface area to the power of 1.219) of patients with tetralogy of Fallot after surgical repair (postop.) as a function of an additional volume load (expressed as percent systemic [SYST.] flow) secondary to pulmonary insufficiency (+PI) or residual ventricular septal defect (+SH), or both. −PI = no PI; −SH = no residual shunt.

TABLE I Vital Statistics, Hemodynamics, Normalized Right Ventricular Volume Variables, and Operative Data

Right Ventricle		Normal	Tetralogy of Fallot			
			Preoperative	Postoperative VL		
				<20%	20–50%	>50%
n	...	100	18	11	13	14
Age (days)	Mean	2,884	1,040	2,885	2,273	2,053
	SD	1,487	878	1,059	1,561	1,137
	Min	30	35	1,579	550	212
	Max	5,518	2,681	4,558	5,929	3,508
	Sign	...	<0.01	NS	NS	<0.05
Height (cm)	Mean	125	86	123	112	109
	SD	27	20	15	22	21
	Min	47	50	104	80	71
	Max	147	114	146	159	135
	Sign	...	<0.01	NS	NS	<0.05
Weight (kg)	Mean	26.0	11.5	23.5	20.1	17.6
	SD	12.0	5.2	5.8	10.5	6.8
	Min	2.6	2.5	16.4	11.0	6.8
	Max	53.6	19.8	34.7	46.6	28.3
	Sign	...	<0.01	NS	NS	<0.01
BSA (m^2)	Mean	0.949	0.504	0.908	0.783	0.731
	SD	0.324	0.189	0.172	0.283	0.219
	Min	0.177	0.181	0.693	0.477	0.357
	Max	1.635	0.761	1.203	1.452	1.020
	Sign	...	<0.01	NS	NS	<0.05
HR (beats/min)	Mean	112	123	105	108	106
	SD	25	32	23	25	15
	Min	63	67	73	75	68
	Max	188	188	143	158	130
	Sign	...	NS	NS	NS	NS
EDV ($ml/m^{2 \cdot 1.1.219}$)	Mean	73.1	65.4	70.3	83.4	96.9
	SD	11.5	19.6	14.8	20.2	27.5
	Min	48.9	32.8	52.7	60.5	65.2
	Max	109.6	100.1	106.3	121.2	148.5
	Sign	...	NS	NS	NS	<0.01
ESV ($ml/m^{2 \cdot 1.219}$)	Mean	26.9	25.3	30.7	38.1	47.8
	SD	6.7	9.0	11.7	9.2	17.9
	Min	9.6	16.9	22.3	25.7	25.2
	Max	44.3	51.6	62.5	55.6	92.3
	Sign	...	NS	NS	<0.01	<0.01

BSA = body surface area; ECC = time of extracorporeal circulation; EDP = end-diastolic pressure; EDV, ESV, SV = end-diastolic, end-systolic and stroke volume, respectively, each normalized for BSA to the power of 1.219; EF = ejection fraction; GRAD = maximal systolic gradient between right ventricle and pulmonary artery; HR = heart rate during angiography; ISCH = time of ischemic arrest; Max = maximum; Min = minimum;

Quantification of pulmonary insufficiency: The degree of pulmonary insufficiency was quantified by roentgen densitometry, a method described before.[9,15] Basically it is a dye dilution technique. After the injection of 5 to 8 ml of contrast medium (Urografin 76%) into the right ventricle, the total amount of this indicator was measured by means of an electronic sampling window covering the entire silhouette of the right ventricle in the lateral x-ray plane stored on magnetic tape. The ratio of changes in amplitudes of the resulting densitogram represents the reflux of dye (deflections at the time of end-diastole minus preceding end-systole) to the amplitude caused by the forward flow (difference of deflections between end-diastole and the following end-systole). It allows the calculation of the regurgitant fraction, that is, the ratio of regurgitant volume over total stroke volume. The excellent accuracy of this method was demonstrated experimentally in comparison with electromagnetic measurements,[16] the standard deviation being 6.5%.

Determination of right ventricular volume load: Comparable degrees of pulmonary insufficiency and residual ventricular septal defect caused a comparable degree of additional volume load on the right ventricle, as judged by the end-diastolic volume (Fig. 1). Therefore it appeared justified to group together patients with pulmonary insufficiency (PI) and those with ventricular septal defect, or both, when considering the effects of volume load on the right ventricle o postoperative patients. Total volume load (VL) was calculatec according to the formula VL = (PI + SH)/(100 − PI) and ex pressed as percent of the systemic flow (SH = left-to-righ shunt across a residual ventricular septal defect).

To compare 2 groups of data the *t* test was used, appro priate for either equal or different variances of the mean.

Results

The results are shown in Tables I and II and Figure 2 to 5. The previously reported normal values[12,13] (95% confidence limits of the mean) are included for comparison.

Before surgical correction: In the 18 preoperative patients mean end-diastolic, end-systolic, and stroke volumes, as well as ejection fraction of the right ventricle were not significantly different from normal while the stroke volume output index was significantly reduced (Fig. 2 and 3). For the left ventricle (17 patients), end diastolic volumes were at the lower limit of the norma range (Fig. 4). Stroke volume, systolic output index, and ejection fraction were significantly lower than norma (Fig. 5). There was no correlation between these volume

TABLE I (continued)

Right Ventricle		Normal	Tetralogy of Fallot			
			Preoperative	Postoperative VL		
				<20%	20–50%	>50%
SV (ml/m$^{2\cdot1.219}$)	Mean	46.2	40.2	39.7	49.1	45.3
	SD	8.3	13.8	8.3	12.6	12.2
	Min	25.5	14.8	26.0	32.8	28.6
	Max	69.0	64.2	53.6	68.3	70.0
	Sign	...	NS	<0.05	NS	NS
EF	Mean	0.633	0.609	0.569	0.513	0.541
	SD	0.068	0.082	0.088	0.065	0.043
	Min	0.478	0.451	0.412	0.378	0.472
	Max	0.850	0.788	0.674	0.614	0.604
	Sign	...	NS	<0.01	<0.01	<0.01
SOI (l/min/m^2)	Mean	4.98	3.99	4.11	4.70	4.54
	SD	1.09	1.29	1.35	1.01	1.46
	Min	2.72	2.25	2.62	2.97	2.90
	Max	7.77	7.93	6.22	6.66	7.68
	Sign	...	<0.01	<0.05	NS	NS
Pmax (mm Hg)	Mean	25.2	92.7	46.0	46.6	43.5
	SD	6.4	12.8	11.5	11.6	8.1
	Min	18.0	70.0	33.0	23.0	30.0
	Max	50.0	119.0	65.0	65.0	60.0
	Sign	...	<0.01	<0.01	<0.01	<0.01
EDP (mm Hg)	Mean	5.9	9.8	9.7	10.4	8.8
	SD	2.0	3.5	4.8	5.0	3.1
	Min	1.0	5.0	4.0	3.0	4.0
	Max	10.0	20.0	22.0	18.0	13.0
	Sign	...	<0.01	NS	<0.01	<0.01
GRAD (mm Hg)	Mean	...	...	19.4	17.6	17.4
	SD	...	...	8.9	9.8	8.2
	Min	...	...	2.0	2.0	4.0
	Max	...	...	30.0	30.0	30.0
ECC (min)	Mean	...	...	74.6	85.8	94.8
	SD	...	...	18.5	27.9	20.2
	Min	...	...	44.0	44.0	70.0
	Max	...	...	105.0	124.0	136.0
ISCH (min)	Mean	...	...	42.8	47.5	52.9
	SD	...	...	11.4	14.3	5.5
	Min	...	...	27.0	20.0	42.0
	Max	...	...	61.0	72.0	62.0

= number of patients in each group; NS = not significant ($p > 0.05$); Pmax = maximal systolic pressure; SD = standard deviation; Sign = statistically significant at given p level compared with normal; SOI = systolic output index; VL = total volume load related to the systemic flow.

variables and tetralogy of Fallot, as judged by the hematocrit (Fig. 6). Peak systolic and end-diastolic pressures were equal in both ventricles.

After surgical correction: After surgical repair in 26 patients end-diastolic and stroke volume of the left ventricle were significantly increased in all 3 volume load groups in comparison with normal values (Fig. 4). Up to a volume load of 20 to 50%, stroke volume and systolic output index of the left ventricle were normal and significantly ($p < 0.01$) increased compared with the preoperative state (Fig. 5). At a volume load of greater than 50%, these variables were significantly greater than normal (Fig. 5). The left ventricular ejection fraction remained significantly reduced postoperatively, but did not decrease further with increasing volume load (Fig. 5). There was a correlation of $r = -0.611$ between left ventricular ejection fraction and patient age at operation (Fig. 7) and $r = -0.407$ between ejection fraction and the time after surgical repair (Fig. 8).

For the right ventricle after surgical repair, end-diastolic, end-systolic, and stroke volumes as well as stroke output index increased with increasing volume load (Fig. 2 and 3). Since end-systolic volume increased progressively more than end-diastolic volume, the resulting ejection fraction decreased with increasing volume load (Fig. 3), being 0.513 ± 0.065 at a volume load of greater than 50%. There was no correlation between right ventricular ejection fraction and the age at operation ($r = 0.150$) or time after surgical repair ($r = -0.0005$) (Fig. 8).

Discussion

The left ventricle before surgical correction: Left ventricular stroke output is a close approximation of but not equal to pulmonary flow in preoperative tetralogy of Fallot with a bidirectional shunt. Nevertheless, the significantly ($p < 0.01$) reduced left ventricular stroke output index (Fig. 5), which has also been observed by others,[1,17] is an expression of diminished pulmonary flow, since the net shunt is right-to-left. On the basis of anatomic studies, end-diastolic volume was found to have a tendency to be smaller than normal,[17,18] which is in agreement with our data (Fig. 4). A significant reduction of angiocardiographically estimated end-diastolic volume was found only by Jarmakani et al.[1,19] in conjunction with a hemoglobin greater than 16 g/100 ml.

TABLE II Vital Statistics, Hemodynamics, Normalized Left Ventricular Volume Variables, and Operative Data

			Tetralogy of Fallot			
				Postoperative VL		
Left Ventricle		Normal	Preoperative	<20%	20–50%	>50%
n	...	83	17	11	8	7
Age (days)	Mean	2,938	2,164	2,161	2,438	2,510
	SD	1,398	831	1,181	1,532	1,356
	Min	29	6	550	569	1,234
	Max	5,191	2,681	4,558	5,727	5,128
	Sign	...	<0.01	NS	NS	NS
Height (cm)	Mean	127	91	110	117	115
	SD	27	22	19	24	19
	Min	48	47	80	80	94
	Max	169	116	146	158	149
	Sign	...	<0.01	<0.05	NS	NS
Weight (kg)	Mean	27.0	13.2	18.4	22.4	19.4
	SD	23.2	5.6	7.1	23.4	9.1
	Min	3.1	2.5	11.0	10.2	10.5
	Max	64.9	20.6	34.7	50.0	38.3
	Sign	...	<0.01	<0.01	NS	NS
BSA (m^2)	Mean	0.971	0.561	0.748	0.846	0.787
	SD	0.330	0.203	0.210	0.311	0.248
	Min	0.192	0.179	0.477	0.462	0.526
	Max	1.664	0.816	1.203	1.487	1.273
	Sign	...	<0.01	<0.05	NS	NS
HR (beats/min)	Mean	107	113	102	114	105
	SD	19	22	21	14	12
	Min	65	83	67	83	88
	Max	167	158	130	130	120
	Sign	...	NS	NS	NS	NS
EDV ($ml/m^{2 \cdot 1.219}$)	Mean	65.2	61.7	73.7	73.3	96.0
	SD	9.6	14.9	10.5	7.8	16.9
	Min	45.2	43.0	56.4	61.7	70.5
	Max	86.0	95.2	96.3	85.0	117.0
	Sign	...	NS	<0.01	<0.05	<0.01
ESV ($ml/m^{2 \cdot 1.219}$)	Mean	18.3	21.0	24.0	26.6	34.9
	SD	5.0	6.4	4.9	5.5	8.8
	Min	9.2	13.7	18.5	20.1	24.1
	Max	29.7	37.3	32.7	35.3	46.6
	Sign	...	NS	<0.01	<0.01	<0.01

Abbreviations as in Table I.

These children may have had a severe form of tetralogy of Fallot.

The significantly reduced left ventricular ejection fraction indicates impaired myocardial function, especially since impedance to ejection in patients with a large interventricular communication is less than normal.[1] It confirms the findings of Jarmakani et al.[1,19] and may be related to histologic alterations, which have been observed in the left ventricular myocardium of patients with tetralogy of Fallot.[20]

The right ventricle before surgical correction: The low stroke output index (Fig. 3) in the presence of a normal end-diastolic volume (Fig. 2) has been related to a right-to-left shunt at the ventricular level.[19] The slightly but not significantly reduced ejection fraction (Fig. 3) indicates that in this group of patients with a mean age of less than 3 years global right ventricular myocardial function is not depressed although systemic pressures are generated at a reduced arterial oxygen saturation.

The left ventricle after surgical correction: Information concerning left ventricular function after surgical repair of tetralogy of Fallot is limited and conflicting. Normal angiographic end-diastolic volume and ejection fraction were noted in children who were operated on successfully without residual defect before the age of 2 years[2] as well as later.[4] By contrast, Jarmakani et al.[1] observed that end-diastolic volume was slightly but significantly increased and that ejection fraction was significantly decreased. Our results are in agreement with the latter findings. Without a significant residual defect, stroke volume and systolic output index became normal (Fig. 5) and pulmonary flow equaled systemic flow. The left ventricle adapted to this increased preload with increased end-diastolic and end-systolic volumes. Both mean values were significantly greater than the preoperative as well as the normal ones (Fig. 4). Since the ejection fraction remained significantly diminished, this finding indicates reduced global left ventricular myocardial function despite normal systemic oxygen saturation and lack of residual defects.

Diffuse and focal myocardial fibrosis observed in preoperative patients of various ages[20] could be the anatomic substrate for the reduced ventricular myocardial function. The rather poor correlation ($r = -0.611$) between left ventricular ejection fraction and age at surgical repair (Fig. 7) does not necessarily sup-

TABLE II (continued)

Left Ventricle		Normal	Tetralogy of Fallot			
			Preoperative	Postoperative VL		
				<20%	20–50%	>50%
SV (ml/m$^{2\cdot1.219}$)	Mean	46.8	40.7	49.7	46.7	61.1
	SD	8.0	9.7	7.8	6.5	12.4
	Min	28.5	25.1	36.1	37.2	46.4
	Max	64.3	58.1	63.7	56.1	80.6
	Sign	...	<0.01	NS	NS	<0.05
EF	Mean	0.719	0.661	0.674	0.638	0.637
	SD	0.063	0.046	0.056	0.061	0.061
	Min	0.589	0.578	0.581	0.555	0.564
	Max	0.852	0.735	0.754	0.736	0.753
	Sign	...	<0.01	<0.05	<0.01	<0.01
SOI (l/min/m^2)	Mean	4.85	3.87	4.70	4.99	6.03
	SD	1.04	0.78	1.06	0.48	1.34
	Min	2.77	2.18	3.09	4.52	3.78
	Max	7.71	5.15	6.20	5.98	8.07
	Sign	...	<0.01	NS	NS	<0.01
Pmax (mm Hg)	Mean	102.5	88.7	92.3	93.6	97.9
	SD	9.4	6.7	14.3	16.1	16.0
	Min	81.0	80.0	72.0	78.0	77.0
	Max	130.0	103.0	123.0	123.0	123.0
	Sign	...	<0.01	<0.05	NS	NS
EDP (mm Hg)	Mean	11.8	11.1	13.3	11.9	14.9
	SD	3.2	5.1	3.4	3.4	2.9
	Min	5.0	4.0	7.0	8.0	10.0
	Max	21.0	25.0	19.0	19.0	19.0
	Sign	...	NS	NS	NS	<0.05
GRAD (mm Hg)	Mean	...	...	17.5	16.8	19.7
	SD	...	...	9.3	6.2	10.7
	Min	...	...	2.0	6.0	6.0
	Max	...	...	30.0	26.0	30.0
ECC (min)	Mean	...	...	89.2	78.8	85.1
	SD	...	...	34.8	15.7	37.6
	Min	...	...	44.0	61.0	44.0
	Max	...	...	136.0	106.0	148.0
ISCH (min)	Mean	...	...	51.1	45.2	40.0
	SD	...	...	11.4	9.0	15.9
	Min	...	...	36.0	33.0	13.0
	Max	...	...	67.0	58.0	54.0

port the suggestion[8] that early operation improves left ventricular myocardial function. A decreasing ejection fraction with age as part of the natural history of this disease may be a contributing factor. Whether further deterioration occurs after surgical repair, particularly in relation to age at operation or residual defects (especially a residual ventricular septal defect), cannot be answered by this study. The low correlation ($r = -0.407$) between left ventricular ejection fraction and time after surgical repair (Fig. 8) does not justify such a conclusion. An increasing volume load resulted in increasing end-diastolic and end-systolic volumes as well as stroke volume output index. The ejection fraction, however, did not decrease further, which suggests that a certain functional reserve is preserved.

The right ventricle after surgical correction: In the group of patients with minimal or no residual defects after operative repair, stroke volume, stroke output index, and ejection fraction were significantly reduced. In the presence of normal end-diastolic and end-systolic volumes this indicates a depressed right ventricular function even in those patients in whom an excellent surgical result could be achieved. These findings are in agreement with those of Burnell et al.[5] and Jarmakani et al.,[6] but differ from those of Graham et al.,[7] who found a normal ejection fraction in similar patients. The age at operation may be an important factor, since increasing myocardial fibrosis has been observed with increasing age in patients with tetralogy of Fallot.[20] The mean age at operation of our patients (5.5 years) is comparable to that of those reported by Graham et al.[7] (4.1 years), while that of the children studied by Burnell et al.[5] was less than 4 years. The latter, however, were operated on during the late 1960s. Further investigations are needed.

Clinical role of postoperative right ventricular volume load: One of the common sequela of surgical repair is a volume load due to a residual ventricular septal defect or pulmonary insufficiency, or both.[21–27] The difficulty in quantifying the degree of pulmonary insufficiency[28] has undoubtedly contributed to the lack of information on the effects of pulmonary insufficiency on the myocardial function of the right ventricle after surgical repair. We determined pulmonary insufficiency with a videodensitometric method[9] in all patients undergoing routine postoperative heart catheterization. The accuracy of this technique has been documented in animal experiments by comparison with electro-

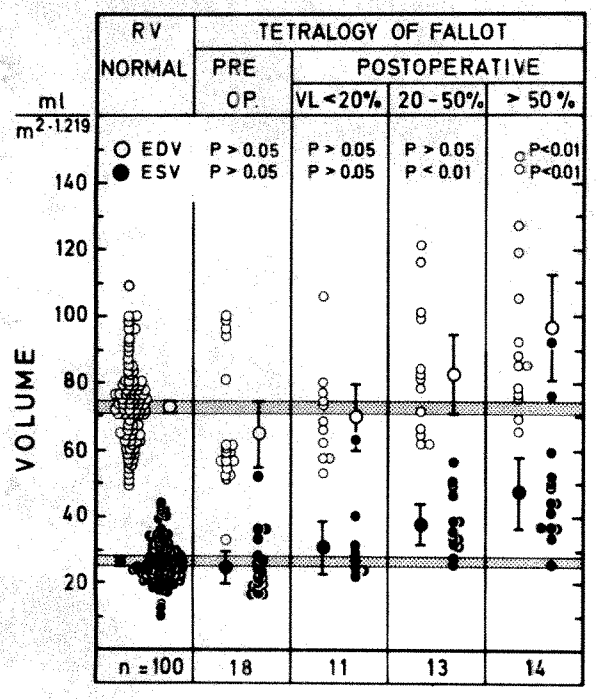

FIGURE 2. Right ventricular (RV) end-diastolic (EDV) and end-systolic (ESV) volumes (normalized for body surface area to the power of 1.219) of pre- and postoperative patients with mean values and 95% confidence limits (**brackets**). The postoperative patients are divided into 3 groups according to an additional right ventricular volume load (VL, expressed as percent of systemic flow) secondary to pulmonary insufficiency or residual ventricular septal defect, or both. Differences with normal data (**shaded areas**) are depicted as p values.

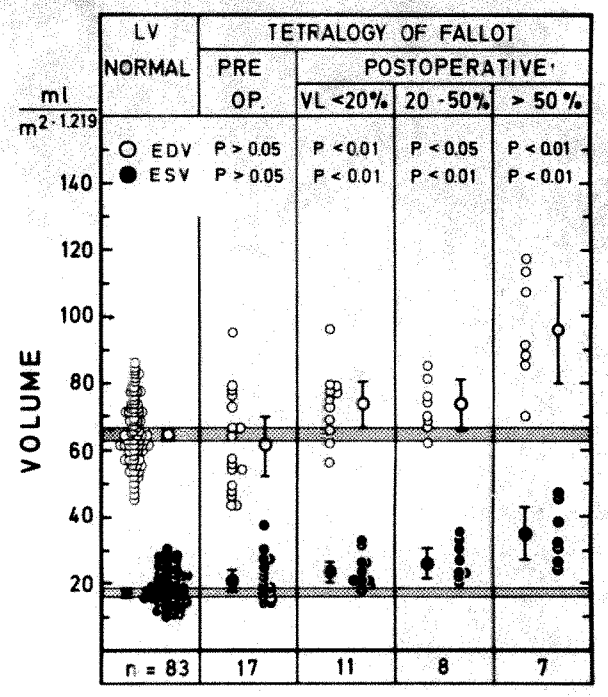

FIGURE 4. Left ventricular (LV) end-diastolic (EDV) and end-systolic (ESV) volumes (normalized for body surface area to the power of 1.219) of pre- (PRE OP) and postoperative patients with mean values and 95% confidence limits. The postoperative patients are divided into 3 groups according to an additional left ventricular volume load (VL, expressed as percent of systemic flow) secondary to a residual ventricular septal defect. Differences with normal data (**shaded**) are depicted as p values.

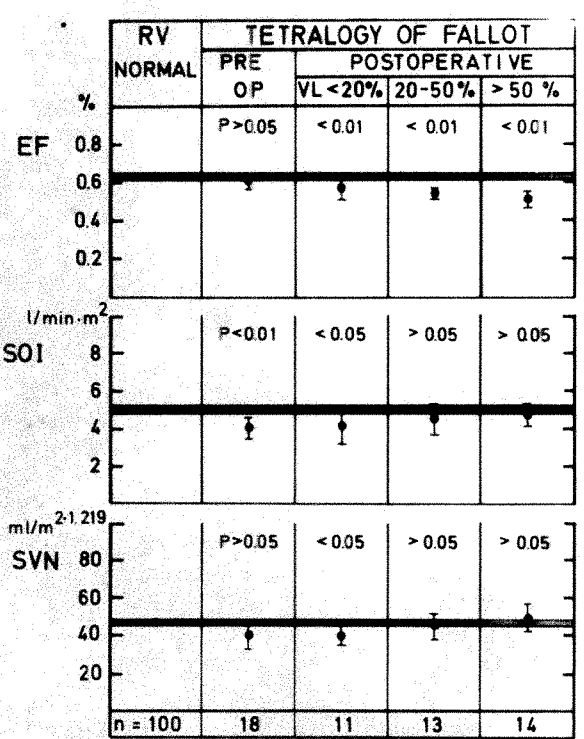

FIGURE 3. Mean values and 95% confidence limits of right ventricular (RV) ejection fraction (EF), systolic output index (SOI), and normalized stroke volume (SVN) of pre- (PRE OP) and postoperative patients. The postoperative patients are divided into 3 groups as in Figure 2.

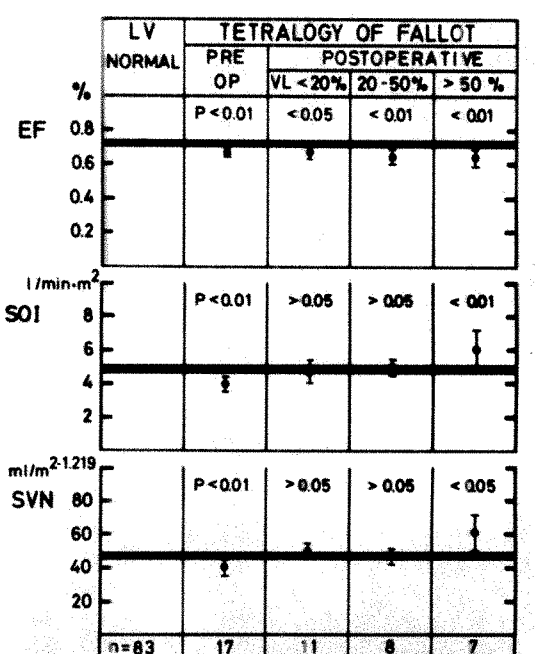

FIGURE 5. Mean values with 95% confidence limits of left ventricular (LV) ejection fraction (EF), systolic output index (SOI), and normalized stroke volume (SVN) of pre- (PRE OP) and postoperative patients. The postoperative patients are divided into 3 groups according to an additional volume load (VL) as in Figure 4.

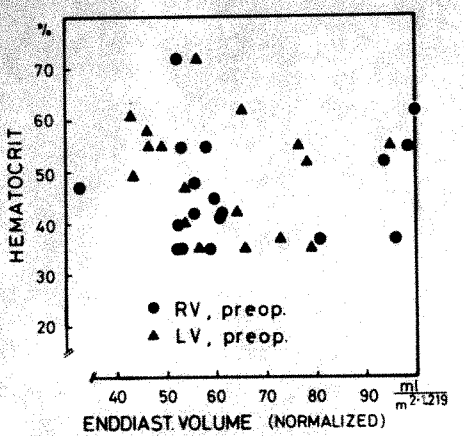

FIGURE 6. Right (RV) and left (LV) ventricular end-diastolic (END DIAST.) volumes (normalized for body surface area to the power of 1.219) of preoperative (PRE OP) patients with tetralogy of Fallot as a function of the hematocrit. There is no correlation.

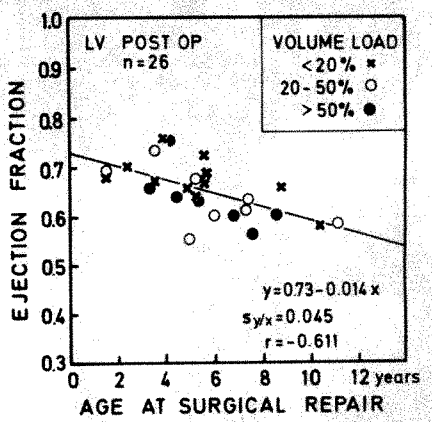

FIGURE 7. Relationships between postoperative (POST OP) left ventricular (LV) ejection fraction and the age at surgical repair. The patients are divided into 3 groups according to an additional volume load (expressed as percent of systemic flow) secondary to a residual ventricular septal defect.

magnetic flow values.[16] Our results in this study were expressed in terms of percent of the systemic flow, thus allowing comparison with the flow across a residual ventricular septal defect.

Similar degrees of additional right ventricular filling in diastole and systole resulted in a similar degree of right ventricular enlargement (Fig. 1). A right ventricle dilated as a result of a ventricular septal defect is not surprising. Graham et al.[29] reported a marked increase in right ventricular end-diastolic size in patients with an isolated ventricular septal defect.

Although the number of patients found to have isolated pulmonary insufficiency or residual ventricular septal defect is small, it seemed justified to assume a similar effect of each lesion on diastolic and systolic volume load. With increasing volume load, end-diastolic and end-systolic volumes increased while ejection fraction decreased. In conjunction with increased end-diastolic pressure this indicates a loss of functional reserve. It is probably related to fibrotic changes secondary to preoperative hemodynamic function,[20] the loss of myocardium by ventriculotomy and infundibulectomy, the presence of a noncontractile patch, and volume overload. The relative contributions of these factors to the functional abnormalities remain difficult to determine. Our data, gained under comparable diagnostic and surgical conditions, suggest, however, that a postoperative volume load on the right ventricle is a decisive factor. It is supported by the studies of Wessel et al.,[30] who showed on the basis of serial exercise testing in mildly symptomatic and asymptomatic patients after surgical repair that isolated pulmonary insufficiency is less well tolerated than isolated residual obstruction. Thus, one must attempt to avoid or minimize postoperative pulmonary insufficiency. This may in part be achieved by a less liberal use of transanular patches. To optimize the size of a necessary transanular patch further quantitative studies are needed, and such studies are underway in our department.

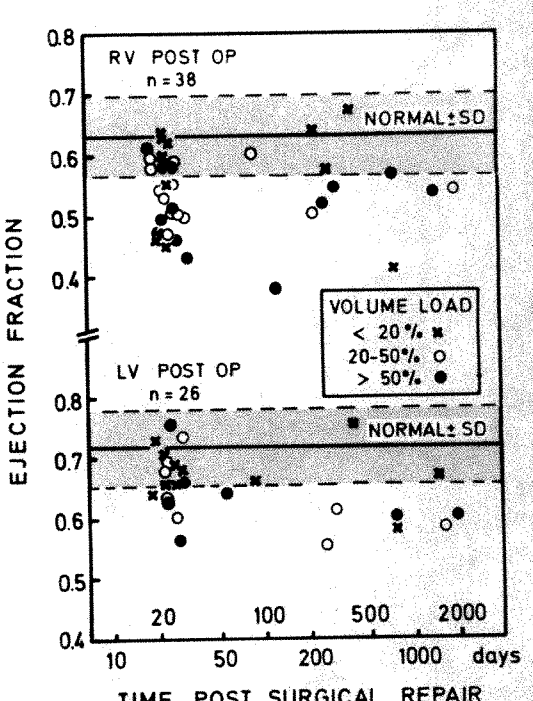

FIGURE 8. Relationship between postoperative (POST OP) ejection fraction and time after surgical repair (logarithmic scale) for the right (RV) and left (LV) ventricle. The patients are divided into 3 groups according to an additional volume load expressed as percent of systemic flow. For the right ventricle there is no ($r = -0.0005$) and for the left ventricle a slight ($r = -0.407$) correlation. SD = standard deviation.

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Currently available antianginal agents...
and how they are most appropriately employed as

BASIC THERAPY FOR THE PREVENTION OF ANGINA PECTORIS*

Report from "Step-Care Therapy for Ischemic Heart Disease"
—a special symposium preceding the annual meeting
of the American College of Cardiology, April 24, 1982.

›psis of the Symposium

l: Nitrates

nitrates both reduce myocar-
xygen demand and increase
ardial oxygen supply, their use
ranted as initial therapy for the
›l of angina pectoris. Dosage
often vary significantly from
ıt to patient, and attention
d be given to ensure that an
ıate dosage level has been
lished.

2: Nitrates and blockers

ngina refractory to maximum-
nitrate therapy, the comple-
ary actions of beta blockers
ıitrates provide a rational ther-
ic modality. At this point a beta
er should be added to the
e regimen.

3: Nitrates and ıum antagonists

ım antagonists have special
ılness in controlling cases
e the myocardial oxygen sup-
diminished by coronary vaso-
m; their use in combination
nitrates is recommended if
2 therapy is unsatisfactory (or if
›atient has variant or vasospas-
ıgina).

Consensus of the Symposium

Nitrates are basic in step-care therapy for ischemic heart disease

Step 1
Stable or unstable angina: Nitrates

Step 2
If not controlled: Nitrates + beta blockers

Step 3
If still not controlled (or in variant angina): Nitrates + calcium antagonists

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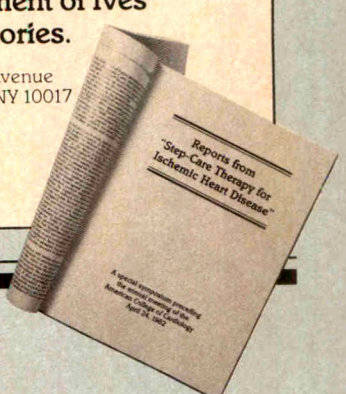

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*ISORDIL has been evaluated as probably effective when taken by the sublingual or chewable route and possibly effective when taken orally for this indication. See Brief Summary on following page.

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"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.
Warnings: Data supporting the use of nitrites and nitrates during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.
Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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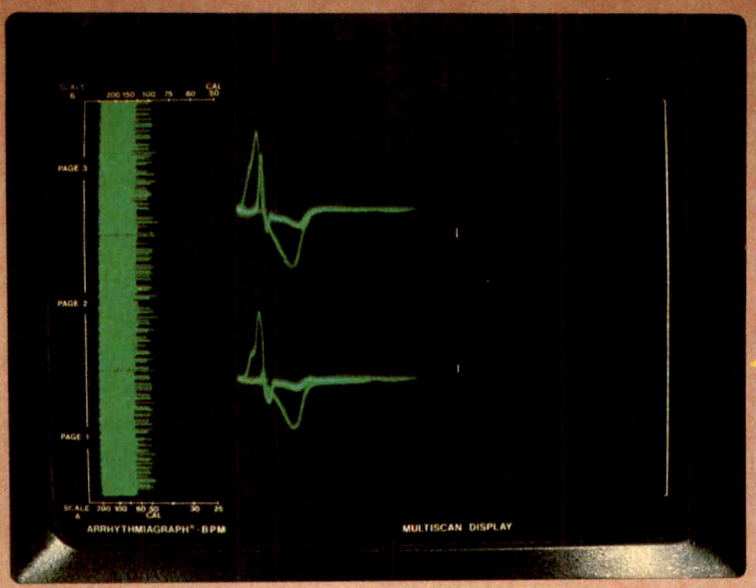

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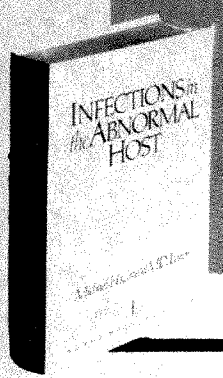

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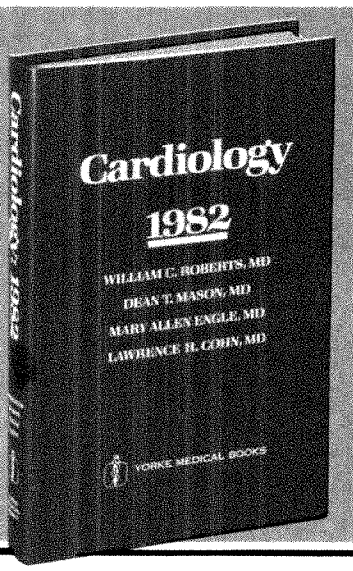

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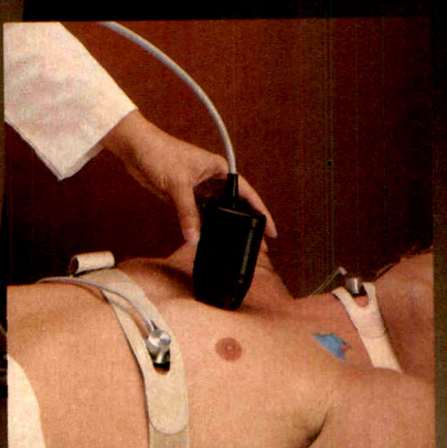

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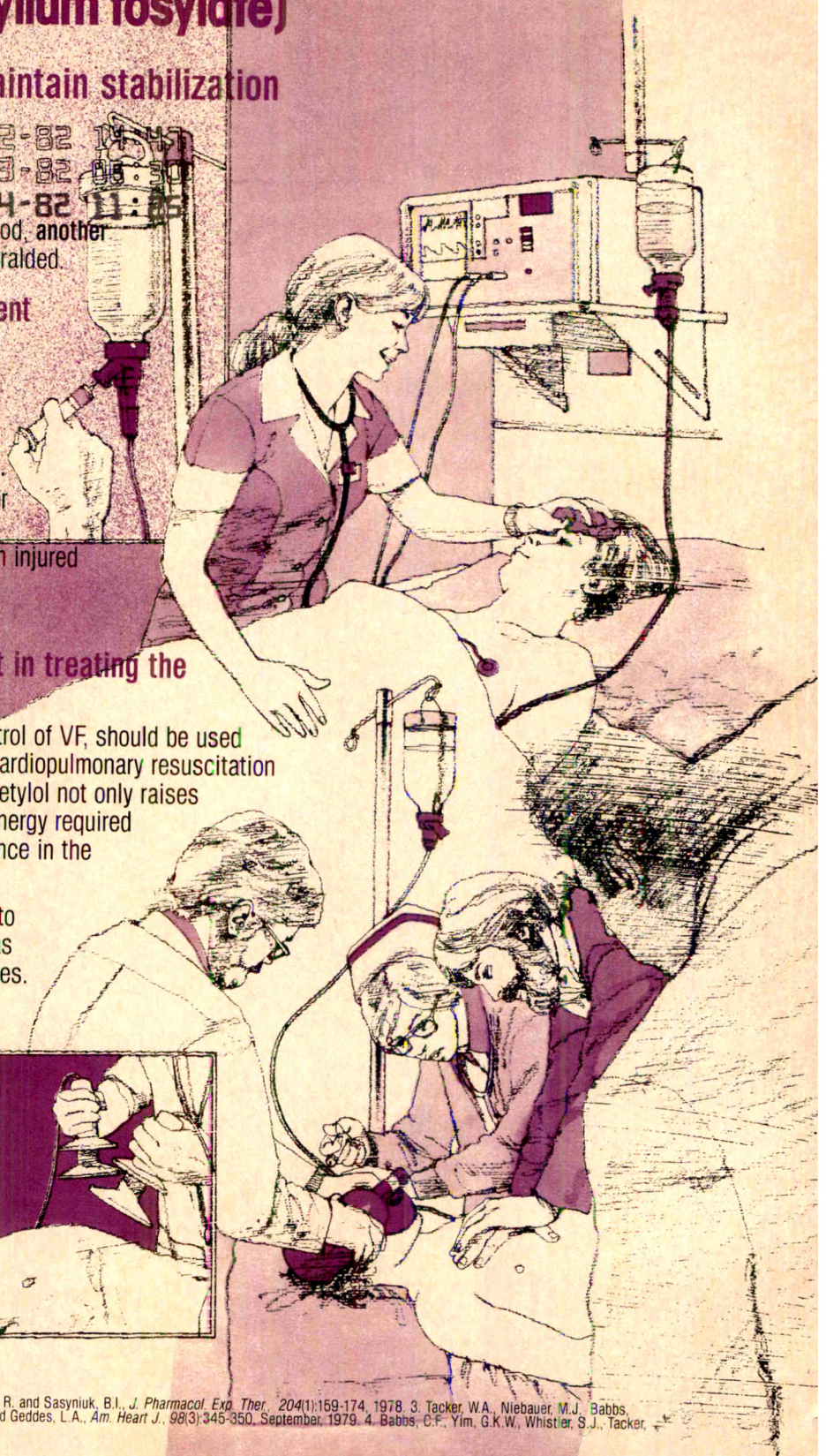

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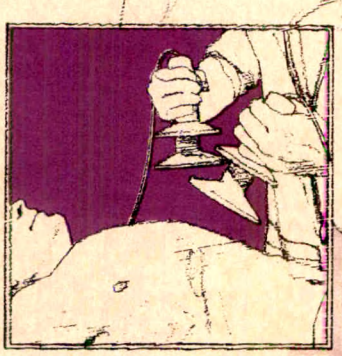

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*based on laboratory animal studies

1. Bacaner, M.B., *Am. J. Cardiol.*, *21*(4):504-512, April, 1968. 2. Cardinal, R. and Sasyniuk, B.I., *J. Pharmacol. Exp. Ther.*, *204*(1):159-174, 1978. 3. Tacker, W.A., Niebauer, M.J., Babbs, C.F., Combs, W.J., Hahn, B.M., Barker, M.A., Seipel, J.F., Bourland, J.D. and Geddes, L.A., *Am. Heart J.*, *98*(3):345-350, September, 1979. 4. Babbs, C.F., Yim, G.K.W., Whistler, S.J., Tacker, W.A. and Geddes, L.A., *Am. Heart J.*, *98*(3):345-350, September, 1979.

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INDICATIONS — BRETYLOL is indicated in the prophylaxis and therapy of ventricular fibrillation.

BRETYLOL is also indicated in the treatment of life-threatening ventricular arrhythmias, such as ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS — There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS — 1. Hypotension: Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, lightheadedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

> Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

2. Transient Hypertension and Increased Frequency of Arrhythmias: Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

3. Caution During Use with Digitalis Glycosides: The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and BRETYLOL (bretylium tosylate) should be avoided.

4. Patients with Fixed Cardiac Output: In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

USE IN PREGNANCY — The safety of BRETYLOL in human pregnancy has not been established. However, as the drug is intended for use only in life-threatening situations, it may be used in pregnant women when its benefits outweigh the potential risk to the fetus.

USE IN CHILDREN — The safety and efficacy of this drug in children has not been established. BRETYLOL has been administered to a limited number of pediatric patients, but such use has been inadequate to define fully proper dosage and limitations for use.

PRECAUTIONS — 1. Dilution for Intravenous Use: BRETYLOL should be diluted (one part BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventricular fibrillation BRETYLOL should be given as rapidly as possible and may be given without dilution.

2. Use of Various Sites for Intramuscular Injection: When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

3. Reduce Dosage in Impaired Renal Function: Since BRETYLOL is excreted principally via the kidney, the dosage interval should be increased in patients with impaired renal function.

ADVERSE REACTIONS — Hypotension and postural hypotension have been the most frequently reported adverse reactions (see Warnings section). Nausea and vomiting occurred in about three percent of patients, primarily when BRETYLOL was administered rapidly by the intravenous route (see Precautions section). Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, i.e., approximately 1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of BRETYLOL administration to these reactions has not been clearly established.

HOW SUPPLIED — NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injection, USP, pH adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. Sterile, non-pyrogenic.

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Please refer to complete prescribing information prior to use.

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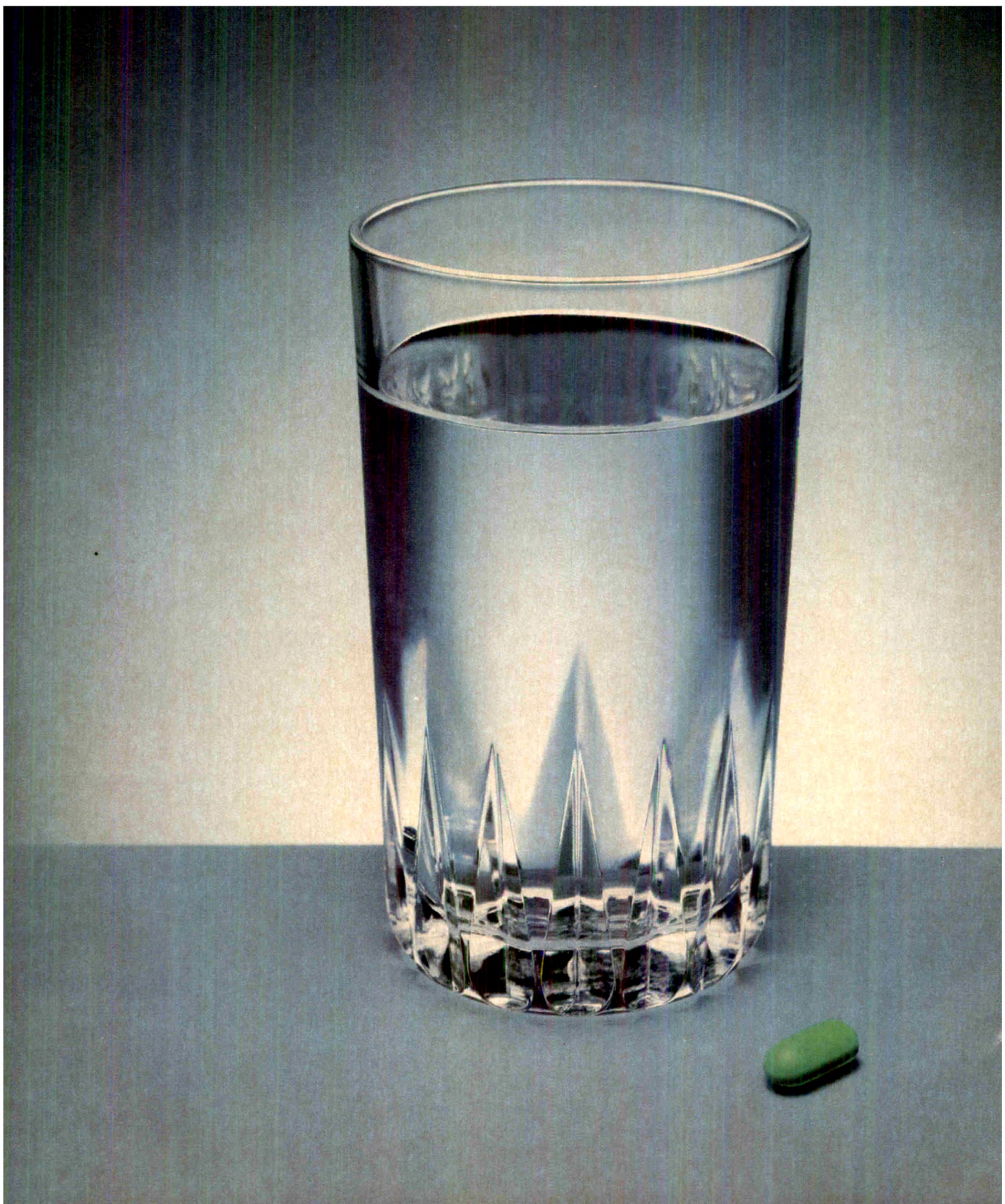

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Indications: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUIDS OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon Cl™-10 mEq (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient years. Kaon Cl-10 mEq should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:
1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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Early Assessment of Hemodynamic Status After Repair of Tetralogy of Fallot: A Comparison of 24 Hour (Intensive Care Unit) and 1 Year Postoperative Data in 98 Patients

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Hemodynamic data obtained in the intensive care unit, immediately after repair of tetralogy of Fallot, were compared with measurements obtained at 1 year postoperative catheterization in 98 infants and children. Eight of 12 patients who had pulmonary artery oxygen saturation of 80% or greater in the intensive care unit had a pulmonary to systemic flow ratio greater than 1.5 at catheterization; all 79 patients who had a pulmonary artery oxygen saturation of less than 80% in the intensive care unit had a pulmonary to systemic flow ratio of 1.5 or less at catheterization. Five of six patients who had a right ventricular outflow tract pressure gradient greater than 40 mm Hg in the intensive care unit had a gradient greater than 40 mm Hg at catheterization; 7 of 61 patients who had a right ventricular outflow tract gradient of 40 mm Hg or less in the intensive care unit had a gradient greater than 40 mm Hg at catheterization. The addition of measurements of right ventricular pressure and the right ventricular to systemic arterial pressure ratio in the intensive care unit did not improve sensitivity in identifying patients with a right ventricular outflow tract gradient greater than 40 mm Hg at catheterization.

Intensive care unit measurement of pulmonary artery oxygen saturation is valuable for determining the presence or absence of a significant left to right shunt after repair of tetralogy of Fallot and should be considered an adjunct to patient management. Intensive care unit measurement of the right ventricular outflow tract gradient identifies patients with a significant right ventricular outflow tract gradient at catheterization but is not highly sensitive.

The results of the present surgical treatment of tetralogy of Fallot have progressed to a point where operative mortality and morbidity are exceedingly low[1,2]; present concerns focus on the timing of surgery,[3–5] variations in surgical technique,[6] and late hemodynamic results.[7,8] Patients who remain symptomatic after surgery often have identifiable persistent structural abnormalities.[9] It has been demonstrated that myocardial performance will be adversely affected by such defects.[10] The purpose of the present investigation was to determine whether patients with residual defects can be identified in the immediate postoperative period so that appropriate treatment can be undertaken without delay. Accordingly, hemodynamic data obtained in the early (24 hour) postoperative period are compared with those obtained 1 year after surgery.

Postoperative assessment of hemodynamic status after repair of tetralogy of Fallot has been routine at this medical center since 1974. Catheters are placed in the left atrium, right atrium, pulmonary artery (through the right ventricular free wall), and a peripheral systemic artery at the time of surgery. Simultaneous determination of the oxygen saturation of blood samples obtained through these catheters allows determination of

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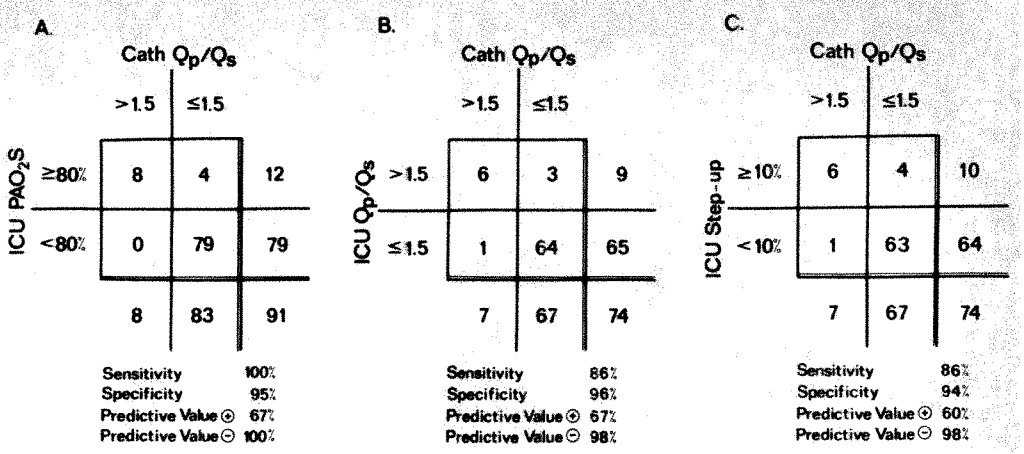
FIGURE 1. "Truth" tables relating immediate postoperative data to pulmonary to systemic flow ratio 1 year after surgery in all 98 patients. **A**, intensive care unit (ICU) pulmonary arterial oxygen saturation (PAO_2S) of 80% or greater as predictive of 1 year postoperative catheterization (Cath) pulmonary to systemic flow ratio (Qp/Qs) greater than 1.5. **B**, intensive care unit Qp/Qs greater than 1.5 as predictive of catherization Qp/Qs greater than 1.5. **C**, intensive care unit step-up in oxygen saturation from right atrium to pulmonary artery of 10% or greater as predictive of catheterization Qp/Qs greater than 1.5.



a pulmonary to systemic flow ratio. A pressure recording of a pullback of the pulmonary artery catheter from the pulmonary artery across the right ventricular outflow tract to the right ventricle allows determination of obstruction at this level. These measurements are routinely performed 24 hours after surgery. In addition, 1 year postoperative hemodynamic evaluation by cardiac catheterization is recommended to all patients who have undergone repair of tetralogy of Fallot.

Methods

Patients: The records of all patients who underwent repair of tetralogy of Fallot at Children's Hospital Medical Center, Boston between January 1974 and June 1979 were examined. Of these, we studied 98 patients for whom data existed pertaining to intracardiac shunting or right ventricular outflow tract obstruction, or both, in the early postoperative period and at 1 year postoperative catheterization. Four patients with additional major intracardiac lesions and 25 who required an external conduit for right ventricular outflow tract reconstruction were excluded. In addition, there are 5 patients for whom no early postoperative data are available and 68 patients who have not undergone cardiac catheterization since surgery.

Early postoperative studies: These were performed 18 to 36 hours after surgery. No patient was receiving supplemental oxygen at a fractional inspired oxygen concentration greater than 0.5. Blood samples were drawn simultaneously from the right atrial, pulmonary arterial, left atrial, and systemic arterial catheters and oxygen saturation measurements were made. Pullback pressure tracings from the pulmonary artery to the right ventricle (or right ventricular pressure tracing alone if the catheter was in the right ventricle) were recorded. The right ventricular outflow tract pressure gradient was determined by subtracting the peak pulmonary artery systolic pressure from the peak right ventricular systolic pressure.

One year follow-up studies: At cardiac catheterization, pulmonary to systemic flow ratios were determined by the Fick principle using pulmonary artery, superior vena cava, and systemic arterial oxygen saturations obtained during the rapid pullback of the catheter from pulmonary artery to superior vena cava while measuring oxygen consumption. If there was no step-up in oxygen saturation but left ventricular angiography revealed a tiny residual ventricular septal defect, the patient was arbitrarily assigned a pulmonary to systemic flow ratio of 1.1. The right ventricular outflow tract gradient was determined by subtracting the peak distal pulmonary arterial systolic pressure from the peak right ventricular systolic pressure recorded during the same catheter pullback.

Analysis of data: "Truth" tables were constructed comparing immediate postoperative data with those obtained at 1 year postoperative catheterization. Immediate postoperative data were compared with the pulmonary to systemic flow ratio and the right ventricular outflow tract gradient determined at cardiac catheterization.

Results

Residual left to right shunts: The immediate postoperative pulmonary to systemic flow ratio, the absolute step-up in oxygen saturation from the right atrium to the pulmonary artery, and the oxygen saturation in the pulmonary artery were compared with the pulmonary to systemic flow ratio at 1 year postoperative catheterization (Fig. 1 and 2). All 3 measurements were highly sensitive in identifying patients with a hemodynamically significant left to right shunt. More data were available for analysis with use of pulmonary arterial oxygen saturation alone because of malfunction of

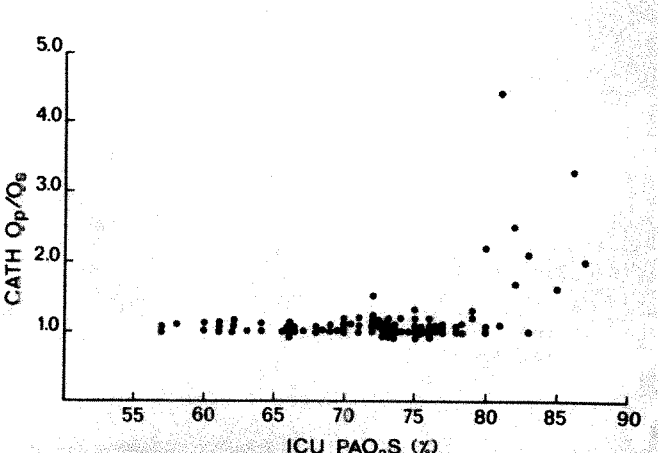


FIGURE 2. Relationship of pulmonary arterial oxygen saturation (PAO_2S) in the immediate postoperative period in the intensive care unit (ICU) to the pulmonary to systemic flow ratio (Qp/Qs) at catheterization (Cath) 1 year after surgery in all patients.

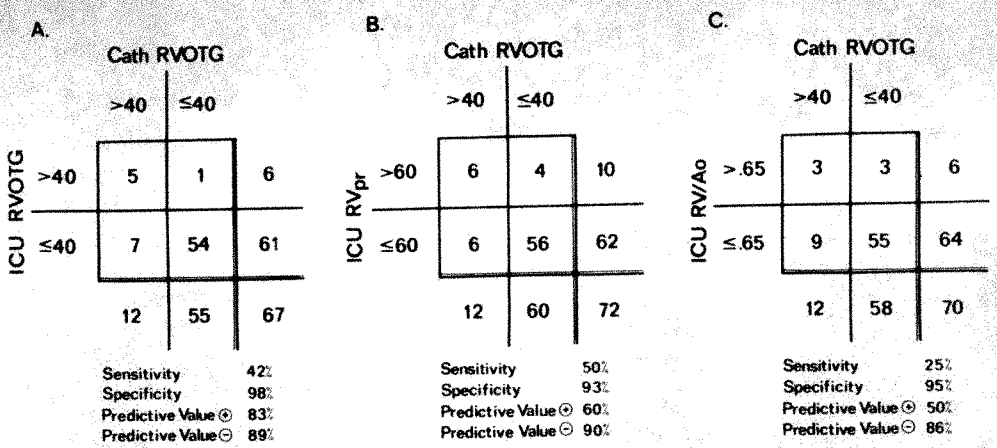


FIGURE 3. "Truth" tables relating immediate postoperative data to the right ventricular outflow tract gradient 1 year after surgery in all patients. **A**, intensive care unit (ICU) right ventricular outflow tract gradient (RVOTG) greater than 40 mm Hg as predictive of 1 year postoperative catheterization (Cath) right ventricular outflow tract gradient greater than 40 mm Hg. **B**, intensive care unit right ventricular pressure (RV_{pr}) greater than 60 mm Hg as predictive of catherization right ventricular outflow tract gradient greater than 40 mm Hg. **C**, intensive care unit right ventricular to systemic arterial pressure ratio (RV/Ao) greater than 0.65 as predictive of catheterization right ventricular outflow tract gradient greater than 40 mm Hg.

some of the right atrial catheters. One patient had a right atrial and pulmonary arterial oxygen saturation of 87% in the immediate postoperative period and a pulmonary to systemic flow ratio of 2.0 at catheterization and was identified as having a significant residual shunt only if the pulmonary artery oxygen saturation alone was evaluated. Table I presents the relevant intensive care unit and catheterization data on the 8 patients with a pulmonary to systemic flow ratio greater than 1.5 at catheterization. With the exception of the 1 patient mentioned (Case 6), all patients could be identified in the intensive care unit by either a pulmonary to systemic flow ratio greater than 1.5, a pulmonary arterial oxygen saturation of 80% or greater, or an increase in oxygen saturation of at least 10%.

Residual right ventricular outflow tract obstruction: The immediate postoperative right ventricular outflow tract gradient, the right ventricular pressure, and the right ventricular to systemic arterial pressure ratio were compared with the right ventricular outflow tract gradient at 1 year postoperative catheterization (Fig. 3 and 4). None of these variables was highly sensitive in identifying patients with significant late residual obstruction. Table II summarizes the pressure data on the 12 patients with a right ventricular outflow tract gradient greater than 40 mm Hg at follow-up catheterization. Only 6 of these patients had evidence of significant residual right ventricular outflow tract obstruction in the immediate postoperative period.

TABLE I Summary of Data on 8 Patients With a Significant Left to Right Shunt (Qp/Qs Greater Than 1.5) at 1 Year Postoperative Catheterization (Cath)

Patient	Cath Qp/Qs	ICU PAO_2S (%)	ICU Qp/Qs	ICU O_2 Step-Up (%)
6	2.0	87*	1.0	0
18	1.7	82*	1.9*	12*
27	3.3	86*	3.6*	26*
69	2.2	80*	. . .	. . .
70	2.5	82*	2.4*	23*
78	1.6	85*	2.1*	15*
93	2.1	83*	1.9*	13*
96	4.4	81*	2.0*	10*

ICU = intensive care unit; O_2 Step-Up = step-up in oxygen saturation from right atrium to pulmonary artery; PAO_2S = pulmonary arterial oxygen saturation; Qp/Qs = pulmonary to systemic flow ratio.
* Values predictive of residual left to right shunt as shown in Figure 1.

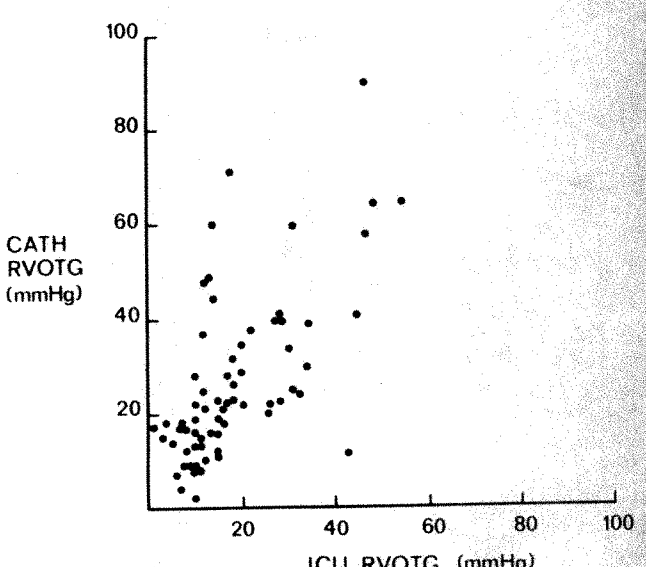


FIGURE 4. Relationship of the right ventricular outflow tract gradient in the immediate postoperative period (ICU RVOTG) to the right ventricular outflow tract gradient 1 year after surgery (CATH RVOTG) in all patients.

Discussion

The principal aims of surgical repair of tetralogy of Fallot are the abolition of intracardiac shunting and the relief of right ventricular outflow tract and pulmonary arterial obstruction. Failure to adequately close an interventricular communication results in left to right shunting if the obstruction to pulmonary blood flow is relieved. The adverse effects of such a shunt after repair of tetralogy of Fallot have been demonstrated.[10] Although the significance of mild to moderate persistent right ventricular outflow tract obstruction has not been clarified, recent evidence suggests that it contributes to ventricular arrhythmias, which in turn have been correlated with late sudden death.[11]

Diagnosis and management of residual postoperative left to right shunt: The detection of a significant left to right shunt in patients immediately after repair of tetralogy of Fallot is often difficult on clinical examination. Systolic and diastolic murmurs associated with reconstruction of the right ventricular outflow tract and some degree of congestive cardiac failure are almost universal in the early postoperative period. Noninvasive diagnostic techniques such as echocardiography and radionuclide angiocardiography lose specificity in the presence of pulmonary regurgitation. The persistence of congestive failure beyond several months indicates a likelihood of significant hemodynamic defects; earlier recognition followed by repair is possible.

The techniques employed in this study were highly sensitive in identifying patients shown to have a pulmonary to systemic flow ratio greater than 1.5 one year after surgery. All 8 patients with a significant shunt at 1 year postoperative catheterization had a pulmonary arterial oxygen saturation of 80% or greater in the intensive care unit. Such shunting can result from incomplete closure of the malalignment ventricular septal defect of tetralogy of Fallot or from the presence of additional defects. We currently recommend early confirmation of shunt size and localization of the defect by cardiac catheterization and left ventricular angiography. Patients shown to have a pulmonary to systemic flow ratio greater than 1.5 undergo closure of the residual defect. The importance of angiographic localization of residual defects was recently stressed by the demonstration that 14% of infants with tetralogy of Fallot have multiple or complicated ventricular septal defects.[12]

Diagnosis of residual postoperative right ventricular obstruction: Our ability to identify patients in the immediate postoperative period who had significant residual right ventricular outflow tract obstruction demonstrated at 1 year postoperative catheterization was not striking. Measurement of the right ventricular outflow tract gradient in the intensive care unit identified only 5 of 12 patients, but with only 1 false-positive result. Measurement of right ventricular pressure or the right ventricular to systemic arterial pressure ratio did not identify significantly more patients but did have a higher rate of false-positive diagnoses. There are several possible explanations for the poor specificity of the measurements. Right ventricular outflow tract gradients measured in the intensive care unit would fail to identify patients with distal pulmonary arterial branch obstruction if the monitoring catheter were in the contralateral or main pulmonary artery. However, one would then expect an elevated right ventricular pressure. This was not always the case (Table II). The failure to observe an elevated right ventricular pressure as well as the low right ventricular outflow tract gradient measured in the intensive care unit in patients with significant obstruction 1 year later may indicate that right ventricular outflow tract gradients increase with time. It is interesting to note that several centers[1,3] employ intraoperative measurement of the right ventricular to systemic arterial pressure ratio as an index of the adequacy of right ventricular outflow tract reconstruction. Our data suggest that this may fail to

TABLE II Summary of Data on 12 Patients With a Significant Right Ventricular Outflow Tract Gradient (Greater Than 40 mm Hg) at 1 Year Postoperative Catheterization (Cath)

Patient	Cath RVOTG (mm Hg)	Cath RVP (mm Hg)	ICU RVOTG (mm Hg)	ICU RVP (mm Hg)	ICU RV/Ao Ratio
5	71	87	18	40	0.41
10	49	61	13	28	0.28
25	41	60	28	49	0.41
40	60	100	31	49	0.43
45	45	76	14	32	0.34
48	65	80	48*	68*	0.86*
53	48	72	12	52	0.51
62	65	85	54*	80*	0.69*
67	90	107	46*	82*	0.66*
78	41	57	44*	64*	0.65*
82	58	70	46*	65*	0.54
96	60	100	14	64*	0.54

ICU = intensive care unit; RV/Ao = right ventricular to systemic arterial pressure ratio; RVOTG = right ventricular outflow tract gradient; RVP = right ventricular pressure.
* Values predictive of residual right ventricular outflow tract obstruction as shown in Figure 3.

identify significant residual obstruction. In addition, others[13] have recently shown that such measurements may be misleadingly high.

Our current recommendations for hemodynamic evaluation of patients after repair of tetralogy of Fallot include (1) measurements of pulmonary arterial oxygen saturation and right ventricular outflow tract gradient in the intensive care unit after surgery, (2) early catheterization of patients with a pulmonary arterial oxygen saturation greater than 80% or a right ventricular outflow tract gradient greater than 40 mm Hg, and (3) catheterization of all patients 1 year after surgery.

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Pediatric Cardiac Catheterization With Same-Day Discharge

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A system was developed for cardiac catheterization in children without overnight hospital stay (called same-day discharge). Over a 4 year period, 233 children (aged 5 weeks to 20 years) had catheterization with same-day discharge, staying an average of 11.8 hours in the hospital. In all but 1, no problems occurred after hospital discharge; 1 child required readmission for psoas tendinitis after retrograde aortography. Same-day discharge was safely applied regardless of the patient's age, diagnosis, and use of systemic heparinization, large-bore sheaths, retrograde arterial catheterization, or cineangiography. The hospital-related cost of pediatric cardiac catheterization was reduced 29% compared with that of the standard 42 hour hospital stay.

Same-day discharge provides attractive elements to the physician and institution involved in cardiac catheterizations, for example: (1) improved medical care by a decrease in the length of hospitalization, (2) a significant reduction in medical costs, and (3) elimination of time pressure in training and teaching as well as therapeutic decision-making. Critical factors for the successful application of same-day discharge are coordination of multiple health care professionals and physician judgment of the patient's clinical status. We speculate that reassessment of other hospital-oriented procedures may foster the development of methods for improving medical care or reducing cost, or both.

In 1976, we posed the question, "Must cadiac catheterization in children require overnight hospital stay?" Theoretical advantages of shortening the length of hospitalization include lessening of psychosocial stress, more efficient use of scarce resoures (such as hospital beds and nurses), and, of course, reduction in the cost of medical care. A system was developed at the San Diego Children's Hospital for admission, cardiac catheterization, and discharge on 1 day (same-day discharge). This system involved the timed interaction of: (1) anesthesia service, (2) cardiac catheterization laboratory, (3) cardiology service, (4) clinical laboratories, and (5) nursing staff.

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Methods

Patients: From January 1, 1977 to December 31, 1980, 645 cardiac catheterizations were performed in children (under 21 years of age) at the Children's Hospital of San Diego (Table I). The study group consists of 418 studies performed on an elective basis (65% of all pediatric catheterizations). Of these, 233 were performed with same-day discharge.

Hospital charts and catheterization logs were reviewed to determine: (1) patient demography, (2) diagnosis, (3) technical details of catheterization, (4) complications/hospital readmission, and (5) elapsed times (admission to catheterization, catheterization procedure, and catheterization to discharge). The decision regarding same-day discharge or overnight hospital stay was made by the physicians performing the catheterization (4 individuals).

Data analysis: The information was coded on IBM punch cards, tabulated, and manipulated on a Burroughs 7800 computer. Chi-square analysis was utilized for comparisons of nominal data (such as demographic or catheterization characteristics of patient groups) and t tests were used for analysis of ordinal data (primarily data measured in time).

TABLE I Pediatric Cardiac Catheterization Experience (1977 through 1980)

	1977	1978	1979	1980	Total
Total catheterizations	134	121	164	226	645
Elective catheterizations	88	82	106	142	418
Same-day discharge	20 (23%)	28 (34%)	72 (68%)	114 (80%)	233 (56%)
Overnight hospital stay	68	54	34	28	185
For specific reason	7	4	9	13	. . .
Without specific reason	61	50	25	15	. . .

Results

Reason for overnight stay versus same-day discharge: Year-by-year analysis of the 233 same-day discharges (Table I) shows a progressive increase in the percentage of the 418 elective catheterizations performed with same-day discharge from 23% in 1977 to 80% in 1980. Of the 418 children, 185 (44%) spent 1 or more nights in the hospital: 114 spent 1 night, 64 spent 2 nights, and 7 stayed 3 or more nights after catheterization. Specific reasons for overnight hospital stay included: (1) fever or emesis in 7, (2) arrhythmias in 7, (3) catheterization limb problems (spasm or thrombus) in 4, (4) cerebral embolus in 3, (5) hypercyanotic spells in 2, and (6) technical or equipment problems in 10. Overnight hospital stay without specific reason occurred in 69% (61 of 88) of elective pediatric catheterization in 1977, compared with only 11% (15 of 142) in 1980.

Clinical differences in the 2 patient groups: Children under 1 year of age stayed overnight more frequently ($p < 0.05$) than having same-day discharge; in the older children there was no significant difference between same-day discharge and overnight hospital stay. Median weight was similar in same-day discharge (13.3 kg) and overnight hospital stay (12.3 kg) groups. Comparing same-day discharge and overnight hospital stay groups by diagnosis, there was a preference to send home children with obstructions but keep overnight those with left-to-right shunts ($p < 0.05$).

Ninety percent (377/418) of the patients had both right and left heart catheterization; a similar number (375/418) received general (ketamine) anesthesia. There were no significant differences between the same-day discharge and overnight hospital stay groups in the approach to the aorta, use of heparin, volume of contrast agent, number of angiograms, or mean sheath size.

Comparing the chronology of catheterization in same-day discharge and overnight hospital stay groups, significant differences ($p < 0.001$) were seen in time before catheterization (5.8 versus 15.5 hours, respectively) and time after catheterization (5.0 versus 19.7 hours, respectively). Time of the catheterization itself was greater in patients staying overnight than in those with same-day discharge in 1977 ($p < 0.003$) and in 1978 ($p < 0.02$); in 1979 and 1980, time of catheterization was not significantly different in the two groups.

Complications: There were no postdischarge complications in 232 of 233 patients with same-day discharge. Specifically, no patient required hospital readmission for bleeding, endocarditis, dehydration, or thromboembolism. No significant hematoma or groin infection was noted in any patient. In 1 child, psoas tendinitis developed after retrograde aortography and the child was readmitted 6 days after catheterization for therapy of the hip discomfort.

Discussion

The basic question we asked was whether the length of hospitalization for pediatric cardiac catheterization could safely be shortened, resulting in lower costs, decreased risk of hospitalization,[1] and reduction of patient and family anxiety. In most major pediatric cardiac centers, the standard approach to cardiac catheterization involves hospital admission on day 1, catheterization on day 2, and discharge that afternoon or on day 3. The reasons for this 2 to 3 day hospital stay are related to: (1) preparatory noninvasive tests before catheterization, (2) work-up of the patient by physicians-in-training, (3) need to perform several catheterizations per day, (4) possibly increased catheterization time due to clinical research or involvement of physicians-in-training, and (5) observation of the patient.

A system for same-day discharge: By coordinating the activities of all those involved in pediatric catheterization (cardiology and radiology departments, nursing, clinical and catheterization laboratories, and anesthesia and cardiology services), a system was developed as outlined in Table II. Initial complete evaluation of the patient, patient and parent education as well as instruction of the physicians-in-training were usually done on an outpatient basis before hospitalization. A 2 hour time frame was adequate for the majority of studies, including those with clinical research protocols (40% of the catheterizations in 1980).

Acceptance of the same-day discharge procedure was immediate in patients and their families but gradual among medical professionals. During the study period

TABLE II Typical Chronology for Catheterization With Same-Day Discharge

Time	Event
07:30	Hospital admission
08:00	Venipuncture for blood tests
08:30	Examination by cardiologist, anesthesiologist, and cardiac nurse
09:30	Noninvasive tests, if necessary
12:00	Catheterization
14:30	Recovery room
16:30	Return to ward; examination by cardiologist
18:30	Discharge

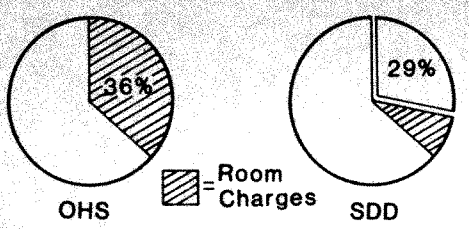

FIGURE 1. Financial savings with same-day discharge. **Cross-hatched areas** indicate room charges with overnight hospital stay (OHS) and same-day discharge (SDD); a 29% reduction in cost is seen with same-day discharge.

(1977 through 1980) the percentage of patients with overnight hospital stay without specific reason decreased from 69 to 11%, indicative of increasing confidence in the safety of the same-day discharge protocol.

Neither the size of the patient nor the diagnosis per se was considered an impediment to same-day discharge. The crucial element was the clinical condition and stability of the patient. No difficulties were encountered with same-day discharge of patients under 1 year of age with compensated heart failure, whether acyanotic or cyanotic, and with or without pulmonary artery hypertension.

Complications: Observation of the groin after catheterization is a common reason for overnight hospital stay. Our experience suggests a reappraisal of this policy. Cardiac catheterization in children almost always involves a femoral venous approach which, beyond the 1st month of life, is virtually risk free. Retrograde arterial catheterization was necessary in 48% of the children. There were 5 arterial complications; in 4 (2 with spasm and 2 with thrombus requiring embolectomy) the problem was immediately evident and the children were kept overnight. The 5th child was discharged the day of catheterization; his subsequent readmission for psoas tendinitis was the only complication in the entire group of 233 children with same-day discharge. Other significant complications of catheterization such as persistent arrhythmia, cyanotic spell, or thromboembolism (total of 13 instances (3%) in 418 elective studies) were readily apparent after the procedure. This experience coincides with earlier reports[2,3] that major complications are usually obvious during or immediately after catheterization.

Constitutional symptoms such as low grade fever, nausea, and emesis are not uncommon after cardiac catheterization. Fever after catheterization has been related to the number of angiograms or the catheter-cleansing techniques, or both, and is not considered indicative of bacteremia.[4,5] Nausea and emesis are occasionally seen after catheterization, probably related to the administration of sedative medications or contrast agents; these side effects are usually short-lived and adequate hydration is temporarily maintained by intravenous fluids. Therefore, we conclude that it is safe to utilize same-day discharge in a child who: (1) is in a hemodynamically stable state, (2) does not require urgent surgery, (3) has no limb complications, and (4) is tolerating oral liquids.

Previous studies: There are no prior published data with which to compare our experience (see Addendum). Rosengart and Sapin of the Kaiser-Permanente Medical Group in Los Angeles (personal communication) have used same-day discharge in over 109 children without complications. Gulde et al.[6] recently presented a large adult experience in an office-located cardiac catheterization laboratory and noted no increase in mortality or morbidity. In 1981 Perrigo et al.[7] reported a 20 month trial of outpatient cardiac catheterization in 224 adults with a 28% decrease in the cost of catheterization.

Hospital costs: Review of our 1980 financial data reveals significant savings realized by same-day discharge (Fig. 1). The average hospital charge for the catheterization procedure plus medications and necessary noninvasive studies averaged $1,093; the room charge for 3 days and 2 nights in the hospital was $615, or 36% of the total hospital bill if the standard approach to pediatric catheterization had been employed. Utilizing same-day discharge, the average time in the hospital was 11.8 hours, which translated to a room charge of $122, a savings of 80% on the room charge and 29% on the total hospital bill. No additional physician charges were created by the use of same-day discharge.

In many centers, children with straightforward defects such as atrial septal defect and coarctation of the aorta have cardiac catheterization and surgery on a single hospital admission. This practice is intended to decrease the length of hospital stay. In a typical case, the child is admitted on Monday, has catheterization on Tuesday, observation on Wednesday, and surgery on Thursday, resulting in a total of 3 nights in hospital before surgery. A same-day discharge approach with subsequent hospital admission results in only 1 night in hospital before surgery, achieving a large reduction in preoperative room charges.

Psychological effects: Of major import is the emotional well-being of the patient and family. Hospitalization and cardiac catheterization generally produce psychological stress in the child because of: (1) anxiety over separation from family, (2) anxiety over unfamiliar (therefore threatening) people, places, and objects, and (3) fear of pain or (in older children) death.[8–10] In addition to the patient's psyche, the family is also under considerable stress. Although preparatory education may alleviate some anxiety,[10,11] the promise that the patient can probably sleep in his or her own bed that night is a major source of relief to both the patient and his family.

Time pressure in teaching and therapeutic decision-making: An additional advantage of the same-day discharge approach to catheterization is the removal of time pressure in teaching and therapeutic decision-making. With the overnight hospital stay approach, the resident or fellow must do the work-up on the patient around the varying schedules of radiology, clinical laboratories, hospital rounds, and the busy in-hospital

staff physician. With the same-day discharge approach, the attending physician and trainee may discuss the findings, rationale for study, and technical considerations well in advance of the study in an unhurried fashion. Finally, the system of catheterization and surgery on 1 admission requires analysis of data, review of angiograms, and team conference during the 1 day between study and operation; the same-day discharge approach with subsequent hospital admission allows consideration of the findings and operative approach as well as possible additional outside consultations without time pressure.

Implications

Elective cardiac catheterization of children with same-day discharge can be performed safely, with consequent decrease in both financial and psychological cost. Even those patients not residing close to the medical center can use a nearby temporary residence as a surrogate home. Our study demonstrates that the goals of reducing medical costs and improving quality of care need not be mutually exclusive. In a recent editorial, Egdahl[12] stated that "many well-established methods of patient care overuse hospitalization." Our data indicate the hospitalization can be shortened for pediatric cardiac catheterization. We believe that reassessment of other expensive hospital-oriented procedures beyond the sphere of congenital heart disease may produce innovative ways to deliver high quality care at a lower cost.

Addendum

During review of this manuscript, Cumming[13] reported a 12 year experience with outpatient cardiac catheterization in children. In 1980, 80% of their children were studied as outpatients, a percentage identical to our same-day discharge experience during the same year. A slightly higher complication rate (1.0%) was noted by Cumming, but most of the complications (9 of 13) did not require hospital admission. The major points on which Cumming and our group concur are (1) the safety of cardiac catheterization in children without overnight hospital stay, and (2) the reduction in stress achieved by this approach.

We differ with Cumming in 2 areas: cost reduction and loss of teaching experience. In contrast to the procedure developed in Canada, no additional charges were created by our same-day discharge approach, which achieved a 29% reduction in hospital charges. Second, we believe that teaching was enhanced by the same-day discharge technique. In most centers, the child receives a work-up by a trainee who has extensive inpatient responsibilities, *all* more urgent than the child admitted for elective catheterization, leaving little time for learning from this exposure. With our system, the same trainee sees the patient in the office, participates in the precatheterization teaching, attends the catheterization itself, reviews the data with the physician performing the catheterization, and attends the regional conference. Thus, teaching appears to be improved rather than impaired by same-day discharge.

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Compression of Intrapulmonary Bronchi by Abnormally Branching Pulmonary Arteries Associated With Absent Pulmonary Valves

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In 3 patients with absent pulmonary valve syndrome and absent ductus arteriosus, the lungs were injected and analyzed postmortem using morphometric techniques. Two patients had tetralogy of Fallot and 1 had D-transposition of the great arteries, the latter being the first autopsy-proved case of absent pulmonary valve with transposition. In addition to the expected dilatation of the central pulmonary arteries and compression of the mainstem bronchi, postmortem pulmonary arteriography revealed a bizarre pattern of hilar branching. Instead of single segmental arteries, tufts of arteries arose which entwined and compressed the intrapulmonary bronchi. In all 3 patients the histologic structure of the pulmonary arteries was abnormal. The elastic lamina of the media of the right and left pulmonary arteries were increased in number outside the lung, but were decreased within the lung. At both sites, the elastic laminae were thickened and fragmented. In the 2 ventilator-dependent patients, there was slight medial hypertrophy and extension of muscle into normally nonmuscular arteries. In 1 of the 2 cases in which the number of bronchial generations was counted, they were decreased, and in the 1 case in which bronchial count was unknown, alveolar multiplication was severely impaired. Therefore, our data may explain why, in some patients with absent pulmonary valve syndrome, relief of compression of the mainstem bronchi alone does not appreciably alleviate or reverse severe respiratory disease.

The absent pulmonary valve syndrome includes absence or rudimentary development of the pulmonary valve leaflets, pulmonary annular hypoplasia, and dilated pulmonary arteries. This syndrome is usually associated with tetralogy of Fallot,[1-14] but can occur with an intact ventricular septum[15-20] and rarely may be associated with D-transposition of the great arteries.[21] There is a high mortality among infants because they usually develop airway obstruction and pulmonary infections which are thought to be due to compression of the mainstem bronchi by the markedly enlarged central pulmonary arteries.

We report herein on 3 infants with the absent pulmonary valve syndrome who were studied postmortem using arteriographic and morphometric techniques. These investigations revealed a previously unreported branching anomaly of pulmonary arteries within the lungs. One of these patients is the first autopsied case of absence of the pulmonary valve with D-transposition of the great arteries.

Methods

Complete postmortem examination was carried out in each case, the heart and lungs being removed en bloc. The cardiac anomalies were diagnosed. The main pulmonary artery was cannulated and injected with a 50°C barium-gelatin mixture at 100 cm water pressure using previously described tech-

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niques.[22] The lung was then inflated through the trachea with 10% formaldehyde at 36 cm water pressure and was fixed inflated for 1 week. Lung volumes were determined by water displacement before and after fixation and arteriograms were taken at 45 kV with a fixed tube distance of 60 cm.

In Cases 1 and 3, the bronchial generations of the lower lobe of the left lung were counted using a dissecting microscope; this was not possible technically in Case 2. The peripheral bronchial branches were reconstructed by means of step sections 50 μm apart. From each case, a 1 cm^2 section was selected at random from each lobe of both lungs. In addition, blocks were taken to provide cross-sections of the main pulmonary artery, the right pulmonary artery, and the segmental axial artery of the right middle lobe. In the case of the latter artery, blocks were examined every 1 cm from the hilum to the periphery.

Alveoli: Alveolar development was evaluated in 3 ways. Alveolar size was assessed as the numbr of alveoli per square centimeter; total alveolar number in each lung was calculated and radial alveolar counts were taken. The latter, according to the method described by Emery and Mithal,[23] consists of drawing a perpendicular line from the center of a respiratory bronchiolus to the periphery, be that a connective tissue septum or a pleural surface. The number of alveoli transected is a measure of alveolar development at any age.

Arteries: In each section, each artery was landmarked according to its accompanying airway (whether preacinar, terminal bronchiolus, respiratory bronchiolus, alveolar duct, or alveolar wall) and examined for structure (whether muscular, that is, completely surrounded by a muscular coat, having both an external and internal elastic lamina; or partially muscular, that is, partially surrounded; or nonmuscular). Using a calibrated eyepiece micrometer, the external diameter of each artery was measured, and for muscular and partially muscular arteries, the thickness of the medial muscular coat was calculated as a percentage wall thickness according to the formula: Percentage wall thickness = (2 × wall thickness/external diameter) ×100. In each field (magnification ×200) the number of arteries and alveoli were counted. Arterial concentration was calculated per unit area and as the number of arteries per 100 alveoli.

Veins: Because veins had not been injected, morphometric data were not available but muscularity was assessed qualitatively.

Bronchi, bronchial arteries, and connective tissue: The bronchi were inspected qualitatively for size and for the presence and amount of cartilage. Bronchial arteries were evaluated qualitatively for number, size, and presence of anastomoses with pulmonary arteries that were judged by whether they had filled with contrast material from the pulmonary artery injection. The amount of connective tissue within the bronchovascular bundle was also assessed.

Normal values: Normal values, obtained in 2 age-matched control infants studied by 1 of us (MR), were similar to those previously reported.[22] To determine those changes in the pulmonary vessels peculiar to the 3 cases in this report, we also compared the findings with those from a 4 month old infant with severe postnatal pulmonary hypertension associated with a double-outlet right ventricle and with those from patients with similar congenital heart defects that we previously reported on.[24,25]

Results

Clinical Findings

Case 1: This male infant was a fraternal twin who was born at term with a birth weight of 3.6 kg after an uneventful pregnancy in a 26 year old gravida 1, para 1. His co-twin was normal. In our patient, cyanosis and marked respiratory distress were noted from birth. A grade 3/6 systolic and diastolic murmur was heard along the left sternal border and the 2nd heart sound was single. The pulses were full and equal, and the liver was firm and palpable 2 cm below the right costal margin. At an FIO_2 of 100%, the arterial blood gases were as follows: pO_2 95 torr, pCO_2 110 torr, and pH 6.6. The infant was intubated and ventilated, and given bicarbonate and digoxin intravenously.

The chest radiograph showed moderate cardiomegaly, diminished pulmonary blood flow, prominent pulmonary arteries, overinflation of the right lung, and underinflation or hypoplasia of the left lung. The electrocardiogram revealed a QRS axis of +120° and right ventricular hypertrophy.

The 2 dimensional echocardiogram was interpreted as showing transposition of the great arteries (S,D,D), a large malalignment type of ventricular septal defect, anterior displacement of the infundibular septum, pulmonary artery overriding of the ventricular septum, massive dilatation of the main pulmonary artery, abnormal pulmonary valve with thickened leaflets and decreased mobility, inability to exclude patent ductus arteriosus because of dilatation of the main pulmonary artery, flattening of the left atrium by the dilated right pulmonary artery, patent foramen ovale, and no evidence of subaortic stenosis.

Cardiac catheterization (Table I) and biplane cineangiocardiography (Fig. 1) were performed when the infant was 8 hours old. The diagnosis of D-transposition of the great arteries with absent pulmonary valve was confirmed and balloon atrial septostomy performed. The infant subsequently became progressively more difficult to ventilate, bilateral pneumothoraces developed requiring chest tube drainage, and the infant died on the 4th day of life.

Case 2: This female infant was born at term with a birth weight of 2.5 kg after an uneventful pregnancy in a 26 year old gravida 1, para 1. She was mildly cyanotic at 16 hours of age. A grade 3/6 harsh systolic and diastolic murmur was heard at the upper left and right sternal borders and the 2nd heart sound was single. Pulses were full and equal and the liver edge was palpable 2 cm below the right costal margin. Chest radiographs showed a right aortic arch, mild cardiac enlargement, diminished pulmonary blood flow, and markedly dilated pulmonary arteries. The electrocardiogram revealed a QRS axis of +90° and biventricular hypertrophy. At an FIO_2 of 80%, arterial blood gases were as follows: pO_2 44 torr, pCO_2 32 torr, and pH 7.39.

A 2 dimensional echocardiogram showed normally related great arteries, a large malalignment type of ventricular septal defect, pulmonary annular hypoplasia, no pulmonary leaflets, and massive dilatation of the main, right, and left pulmonary arteries.

Cardiac catheterization and angiocardiography at 2 days of age confirmed the diagnosis of tetralogy of Fallot with an absent pulmonary valve. The coronary artery anatomy was normal and no ductus arteriosus or ductus diverticulum was seen.

TABLE I Hemodynamic Findings at Cardiac Catheterization

Hemodynamic Measurements	Case 1	Case 2			Case 3
		Study I	Study II		
	FIO_2 0.2	FIO_2 0.2	FIO_2 0.2	FIO_2 1.0	FIO_2 0.8
Oxygen saturation (%)					
SVC	53	63	52	55	66
PA or RV	70	78	67	92	59
PV	98	94	84	96	94
Ao	72	87	82	96	. . .
Pressure (torr)					
RA	6	2	5	6	11
PA or RV (S/D)	(71/8)	(82/6)	37	34	(63/11)
LA	6	3	5	8	11
Ao	57	65	86	90	. . .
Arterial blood gas tension (torr)					
PO_2	24	47	51	287	. . .
PCO_2	33	25	31	43	. . .
pH	7.47	7.40	7.42	7.44	. . .
Flow (liters/min/m^2)					
Pulmonary	. . .	. . .	7.0	10.0	. . .
Systemic	. . .	. . .	3.6	2.2	. . .
Resistance (torr/liters/min/m^2)					
Pulmonary	. . .	. . .	4.6	2.6	. . .
Systemic	. . .	. . .	22.5	38.2	. . .

Ao = aorta; FIO_2 = fraction of inspired oxygen concentration; PA = pulmonary artery; PV = pulmonary vein; RA = right atrium; RV = right ventricle; (S/D) = systolic/diastolic; SVC = superior vena cava; — = mean value; . . . = value not obtained.

Mild congestive heart failure was treated with digoxin and diuretics. Although the infant initially responded well enough to be discharged from the hospital, she failed to thrive and was readmitted at 10 weeks of age weighing slightly less than her birth weight. Repeat cardiac catheterization revealed a large left-to-right shunt, and pulmonary venous desaturation suggesting lung disease.

Surgical repair was undertaken the following day using deep hypothermic circulatory arrest. The aneurysmally dilated main pulmonary artery was incised and tapered. A pericardial patch was placed across the pulmonary annulus. The ventricular septal defect was closed with a Dacron® patch and a patent foramen ovale was sutured. After an initially satisfactory postoperative course, the patient had an episode of sudden unexplained bradycardia and hypotension from which she could not be resuscitated.

Case 3: This female infant was born at term with a birth weight of 3.9 kg after an uneventful pregnancy in a 24 year old gravida 2, para 2; she was cyanotic 15 minutes after birth and was referred to the Deutsches Herzzentrum Munchen in Munich, West Germany. A grade 3/6 systolic and diastolic murmur was heard all over the precordium and the 2nd heart sound was single. Pulses were full and there was no hepatosplenomegaly. Chest radiograph showed a left aortic arch, normal heart size, dilated hilar pulmonary arteries, and decreased

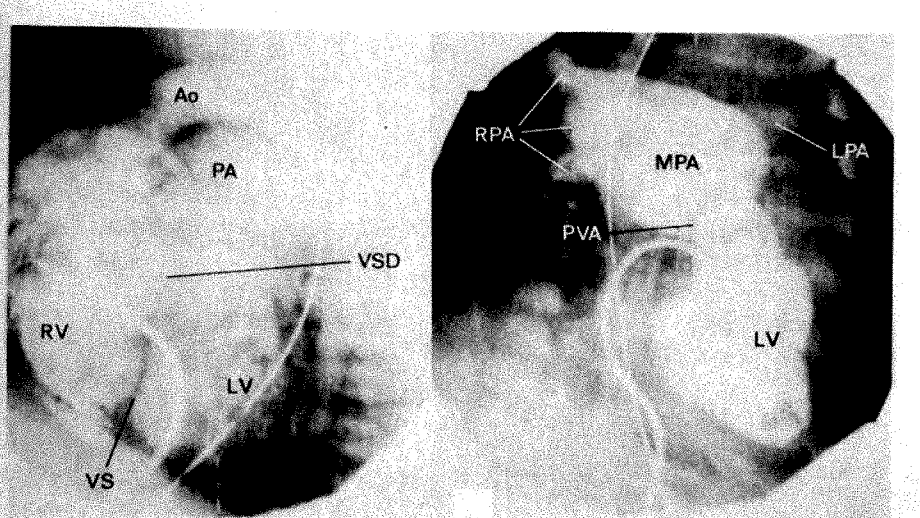

FIGURE 1. Left, lateral projection of the selective right ventricle (RV) injection. Transposition of the great arteries (TGA), marked dilatation of the pulmonary artery (PA), and right-to-left shunting of contrast medium through the large subpulmonary ventricular septal defect (VSD), the morphologically left ventricle (LV), and the ventricular septum (VS) are seen. **Right,** angulated right anterior oblique projection of selective left ventricle injection showing a somewhat narrowed pulmonary valve annulus (PVA) and aneurysmal dilatation of the main pulmonary artery (MPA), right pulmonary artery (RPA), and left pulmonary artery (LPA). Ao = aorta.

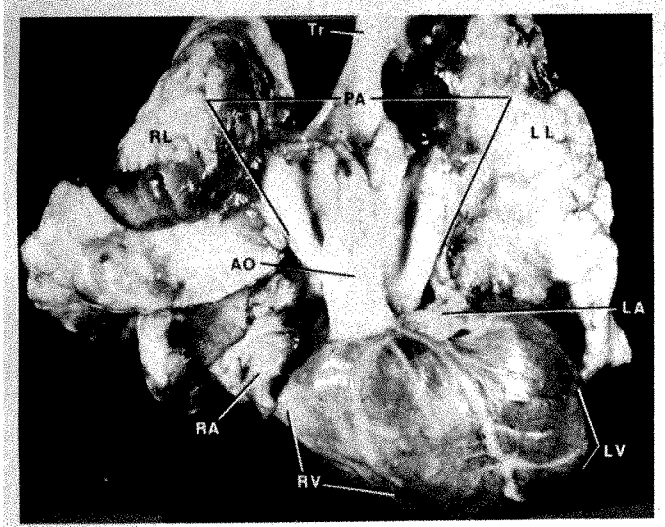

FIGURE 2. Case 1. Heart and lung specimen, external frontal view. The ascending aorta (Ao) arises from the morphologic right ventricle (RV) to the right of the enormously dilated pulmonary artery (PA). The pulmonary artery originates in the morphologic left ventricle (LV), to the left and posterior relative to the plane of the anterior descending coronary artery, which indicates the location of the interventricular septum. LL and RL = left and right lungs, respectively; Tr = trachea.

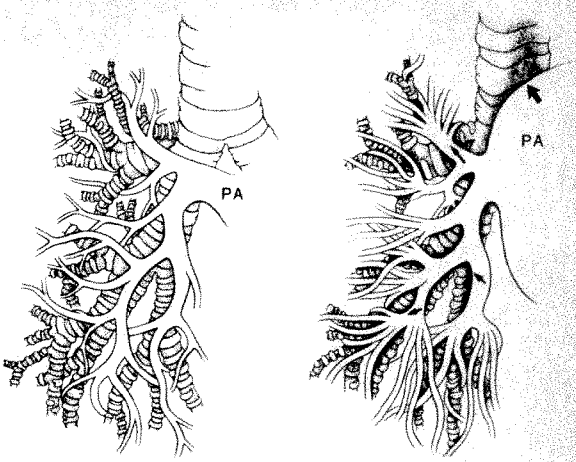

FIGURE 3. Diagram of (**left**) the normal pulmonary artery branching and (**right**) the abnormal pattern seen in our cases of absent pulmonary valve syndrome. Observe the tufts of vessels emerging at the segmental artery level which entwine with the bronchi. **Arrow** denotes large right pulmonary artery compressing the right mainstem bronchus.

peripheral vascular markings. Because of initial hypoxemia, hypercarbia, and acidosis, the infant was placed on a respirator. Arterial blood gases on the ventilator at an FIO_2 of 80% were as follows: pH 7.38, pO_2 38, and pCO_2 42 torr. Cardiac catheterization at 4 days of age confirmed the clinical diagnosis of tetralogy of Fallot with absent pulmonary valve. No ductus arteriosus or ductus diverticulum was seen. The infant became progressively more difficult to ventilate, had recurrent pneumothoraces, and died at 3 months of age.

Postmortem Findings

Gross morphology: **Case 1:** Bilateral pneumothoraces were found at autopsy. Both lungs were distended with air and bullae were present (Fig. 2); the left lung appeared disproportionately smaller than the right. Situs solitus of the viscera and atria (S) was apparent, as well as D-loop (noninverted ventricles [D]), and transposition of the great arteries with the aortic valve lying to the right (dextro or D) relative to the pulmonary valve (S,D,D). The pulmonary artery and branches were markedly dilated; the left ventricle was judged greatly enlarged.

The venae cavae and coronary sinus opened normally to the right atrium. A large tear in the septum primum was seen, evidently produced by balloon atrial septostomy. The tricuspid valve was normal and the right ventricle was hypertrophied. The infundibular septum was displaced anteriorly and to the right of the ventricular septum, resulting in a malalignment infundibuloventricular type of ventricular septal defect. The subaortic infundibulum was not stenotic. The aortic arch was left-sided, its branches were normal, and no ductus arteriosus was present. Typical of D-transposition of the great arteries there was pulmonary-mitral fibrous continuity. The pulmonary annulus was only slightly stenotic. The pulmonary valve leaflets were severely distorted, myxomatous, and hypoplastic. Therefore, although present anatomically, they were virtually absent functionally.

Cases 2 and 3: Systemic venous return, right atrium, and tricuspid valve were normal. The infundibular septum was displaced rightward and anteriorly relatively to the ventricular septum, resulting in an infundibuloventricular type of ventricular septal defect, and the right ventricle was hypertrophied. The pulmonary annulus was stenotic and pulmonary leaflets were not identified. The main, right, and left pulmonary arteries were massively dilated. The pulmonary veins, left atrium, mitral valve, left ventricle, aortic valve, and coronary arteries were grossly unremarkable. The aortic arch was right-sided in Case 2 and left-sided in Case 3. A ductus arteriosus or ligamentum arteriosum was not found in either case.

Morphometric findings in the lung (Table II): *Lobation* of the lungs was normal in all 3 cases. *Lung volumes* (fixed, inflated, right and left) in Cases 1 and 2 were within normal limits when compared with controls (Table II), even though on opening the chest in Case 1, the right lung and left upper lobe appeared enlarged and the left lower lobe seemed smaller than normal. In Case 3, in both lungs, the inflated volumes were greatly increased.

Alveolar development was normal in Case 1, but in Case 2 alveolar number was less than in the control and in Case 3 alveolar size was increased (Table II).

The main, right, and left pulmonary arteries were very enlarged in all 3 cases. The right and left pulmonary arteries were 3 to 4 cm in diameter and where they crossed the main bronchi the latter were compressed

TABLE II Results of Morphometric Examination of Lung

	Lung Volume (ml)		Bronchial Generations, Left Lower Lobe	Alveoli/ cm^2	Total Alveolar Number $\times 10^6$	Arteries per 100 Alveoli	Artery Size (μm)			Arterial Wall Thickness (% External Diameter)						Extension of Muscle		
	Right	Left					TB	RB	AD	50–100 μm	100–150 μm	150–200 μm	200–400 μm	400–600 μm	600–800 μm	RB_m	AD_p	AW_p
Case 1 (4 days)	68	42	18	10,980	44	5	193 ±4	118 ±14	40 ±1	5.0 ±0.6	3.0 ±0.8	3.4	3.0	2.1 ±.5	1.7 ±0.3	100	100	0
Case 2 (4 mo)	100	96	. . .	7,700	35	9	221 ±39	169 ±3	44 ±3	7.0 ±0.5	5.8 ±0.2	3.9 ±0.2	4.7 ±0.1	3	1.4	30	18	0
Case 3 (3 mo)	298	183	26	2,727	66	7.7	172	115 ±10	67 ±3	7.7 ±0.5	4.4 ±0.5	6.0 ±0.9	3.4 ±0.4	3.4 ±0.4	3.8	82	85	33
Control 1 (4 days	68	. . .	24–26	11,375	29*	7.7†	152 ±10	84 ±7	65 ±6	4.5 ±0.8	3.4 ±0.2	3.0 ±0.5	4.4 ±1.3	4.4 ±0.5	5.7	43	0	0
Control 2 (4 mo)	162	108	24–26	11,315	77	6.3	183 ±17	100 ±7	70 ±6	4.6 ±0.3	3.3 ±0.3	3.1 ±0.6	2.9 ±0.1	3.8 ±0.5	5.4	67	18	0
CHD +PH (3 mo)	66	60	24–26	15,000	66.5	3.3	235 ±35	100 ±20	44 ±3	16.5 ±1.5	10 ±3.3	10.5	9.0 ±1	9.5 ±0.5	11.3	100	100	100

AD = alveolar duct level; CHD + PH = congenital heart defect + pulmonary hypertension; m = % of arteries fully muscularized; p = % of arteries partially muscularized; RB = respiratory bronchiolus level; TB = terminal bronchiolus.
* Based on an assessment of right lung volume only. † lower limit of normal based on published data.

(Fig. 3). These pulmonary arteries outside the lung had histologic evidence of an increased number of elastic laminae. The number of elastic laminae was twice normal in Cases 1 and 2, but only mildly increased in Case 3 (Table III). In all 3 patients, the individual elastic laminae were thick, fragmented, and arranged haphazardly as well as concentrically around the vessel. In absolute terms the vessel wall was thicker than normal (0.7 mm), but relative to the external diameter of the vessel, the wall thickness was normal (wall thickness 2%).

The intrapulmonary arteries were abnormal in all 3 cases. In Case 1 no lobar branches could be identified. The segmental arteries seemed to arise directly from the right and left pulmonary arteries (Fig. 4). In Cases 2 and 3 short lobar arteries were identified. Rather than single segmental arteries, tufts of vessels arose in all 3 cases (Fig. 4 and 5). In Cases 1 and 3 each individual artery was similar in size and each was slightly larger than a branch of a normal segmental artery. However, in Case 2 the arteries were not uniform in size, some being larger than normal and others smaller. In this patient, some

FIGURE 4. Postmortem arteriogram from (**top**) a 4 day old control infant and (**bottom**) a 4 day old patient with absent pulmonary valve syndrome (Case 1). Observe the tufts of vessels in both right and left lungs in the latter case.

TABLE III Number of Elastic Laminae of Preacinar Arteries

	Right Pulmonary Artery	Lobar Artery	Segmental Artery			Fragmentation	Thickening
			Origin	50%	75%		
Case 1 (4 days)	54	. . .	8	4	3	++	+
Case 2 (4 mo)	54	6	5	4	3	++	+
Case 3 (3 mo)	26	. . .	8	4	3	++	+
Control 1 (4 days)	21	10	8	7	4	. . .	. . .
Control 2 (4 mo)	21	14	8	7	4	. . .	. . .
CHD + PH (3 mo)	21	10	10	7	4	. . .	++

50%, 75% = distance from hilum to periphery; + = present; ++ = severe; CHD + PH = congenital heart defect + pulmonary hypertension.

of the vessels formed large loop anastomoses (Fig. 6, top). In each case the abnormal segmental arteries had few side branches. They continued toward the periphery with little change in size, entwining and compressing the bronchi they accompanied. The bronchi were distorted and flattened rather than reduced in size (Fig. 6, bottom). If the normal intrapulmonary arterial branching pattern resembles a birch tree, in these cases it is comparable to a weeping willow (Fig. 3 to 5). Although at the segmental level the total number of arteries was increased, at the periphery of the lung the number of arteries was virtually normal. Microscopically, the intrapulmonary arteries at the segmental level were of normal wall thickness but the elastic laminae were normal or slightly reduced in number, irregularly thickened, and fragmented (Fig. 7).

The intraacinar pulmonary arteries were mildly enlarged in all 3 cases, but their number in relation to the alveolar number was normal (Fig. 8, top). In all cases the wall thickness of the normally muscular arteries was appropriate or minimally increased. However, in Cases 1 and 3, there was abnormal extension of muscle into very small peripheral arteries at alveolar duct and wall levels, which normally are nonmuscular.

The *bronchi* were normal in structure and appropriately cartilagenous in all cases, despite their distorted appearance (Fig. 8, bottom). However, in Case 1 we documented a reduced number of bronchial genera-

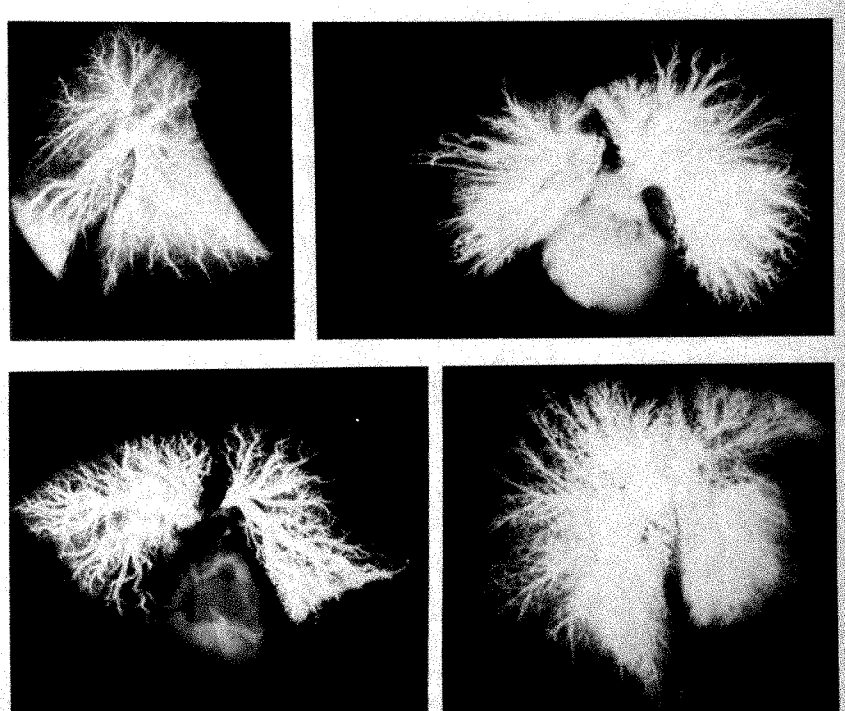

FIGURE 5. Top, postmortem arteriogram from a 4 month old control infant (**left**) and a 4 month old infant with the absent pulmonary valve syndrome (Case 2) (**right**); compared with Case 1, the vessels in Case 2 are less uniform in size and even form loops. **Bottom,** postmortem arteriogram from a 3 month old infant with double-outlet right ventricle and pulmonary hypertension (**left**) and a 3 month old infant with the absent pulmonary valve syndrome (Case 3) (**right**). In the former, the pulmonary arteries have a normal branching pattern but are dilated centrally, tortuous, and narrowed peripherally. In the latter, the pulmonary arteries are markedly increased in number from the hilum.

tions. The bronchial arteries appeared normal and there was no excessive connective tissue in the bronchovascular bundle.

The pulmonary veins were unremarkable in size, wall thickness, and number in all cases.

Comparison with postnatal pulmonary hypertension: The preceding pulmonary morphometric findings in these 3 patients with the absent pulmonary valve syndrome were compared with those of appropriate age-matched controls (Tables II and III) and also with those of a 3 month old infant with double-outlet right ventricle and postnatal pulmonary hypertension whose lungs were studied postmortem in the same manner. The findings in this infant were similar to those observed and previously reported in others with congenital heart defects and postnatal pulmonary hypertension, for example, ventricular septal defect.[24,25] The pulmonary arteries branched normally from the hilum to the periphery. The pulmonary arteries were dilated at the hilum, but narrower than normal peripherally (Fig. 5, bottom). Microscopically, the medial wall thickness was increased. The elastic laminae were normal in number but much thicker than normal and not fragmented (Fig. 7). The intraacinar arteries were smaller and fewer than normal. The wall thickness of arteries that normally are muscular was greatly increased and there was marked extension of medial muscle into peripheral arteries that normally are nonmuscular.

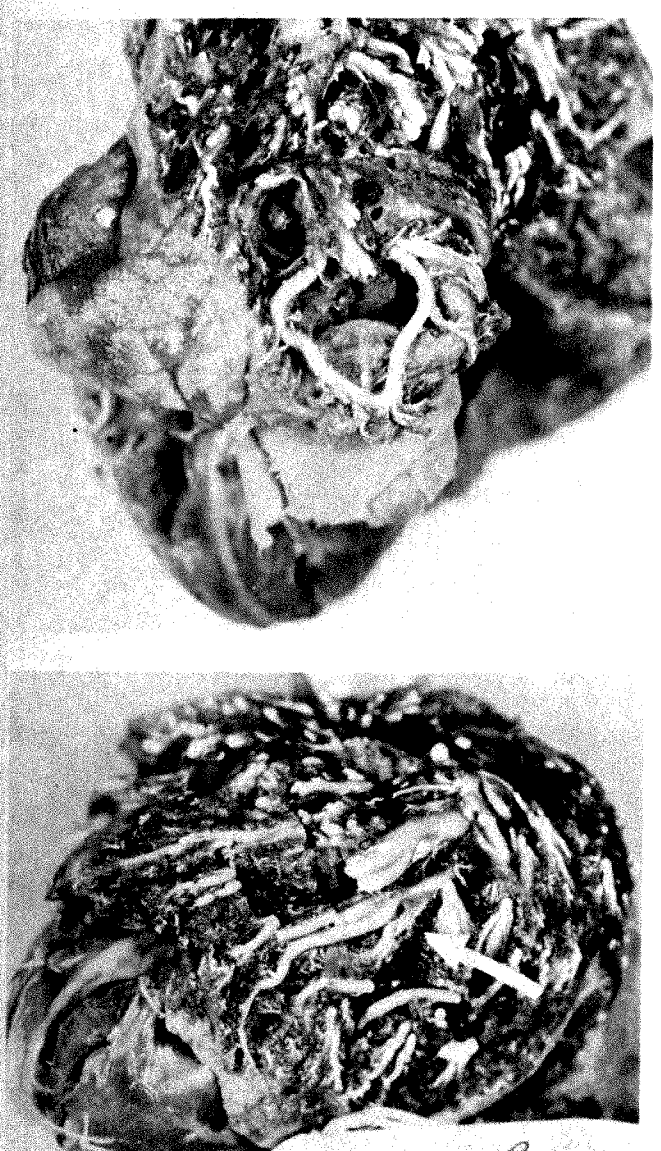

FIGURE 6. Top, dissected lung in Case 2 showing an arterial-to-arterial loop anastomosis, as seen on the postmortem arteriogram. **Bottom,** also in the dissection of the lung in Case 2, a bronchus was compressed between 2 dilated arteries (**arrow**).

Discussion

In this report we describe for the first time the abnormal and rather bizarre branching pattern of the hilar pulmonary arteries in patients with the absent pulmonary valve syndrome and document the first autopsy-proved case of the absent pulmonary valve syndrome in association with D-transposition of the great arteries.

In previous morphologic studies of the absent pulmonary valve syndrome a search was often made for an intrinsic abnormality in the wall of the dilated central pulmonary arteries (main, right, and left). Only some investigators found structural abnormalities, typically consisting of thickening and fragmentation of the elastic laminae and lack of ground substance within the media. In many of these cases, it is not clear whether the patients had, in addition to an absent pulmonary valve, absence of the ductus arteriosus. This combination seems to be associated with the most severe dilatation of the central pulmonary arteries. Our 3 patients all had this combination, and in all the walls of both the extra- and intrapulmonary arteries showed structural abnormalities but of different severity.

It is not known whether the abnormal branching pattern of the hilar pulmonary arteries that we observed in these 3 cases occurs in all patients with the absent pulmonary valve syndrome. Abnormal branching should be suspected in all but may well be found most often in those who also lack a ductus arteriosus. That abnormal pulmonary artery branching has not been reported previously is not surprising. The introduction of Short's technique[26] of postmortem pulmonary arteriography is relatively new and not a routine part of the postmortem examination in many hospitals. Also, cineangiocardiographic studies have in the past been concerned mainly with the central pulmonary arteries (main, right, and left), the ventricular septum, the infundibulum, and the pulmonary valve region. Little attention has been focused on the arteries within the lung. This was certainly true for the studies in these 3 patients. However, it should be possible to diagnose this anomaly of hilar branching by means of routine cineangiocardiography.

Embryology: At first it could be considered that intrapulmonary arteries appear to arise in bunches only because of incorporation of the higher generation vessels into the aneurysmally dilated central pulmonary arte-

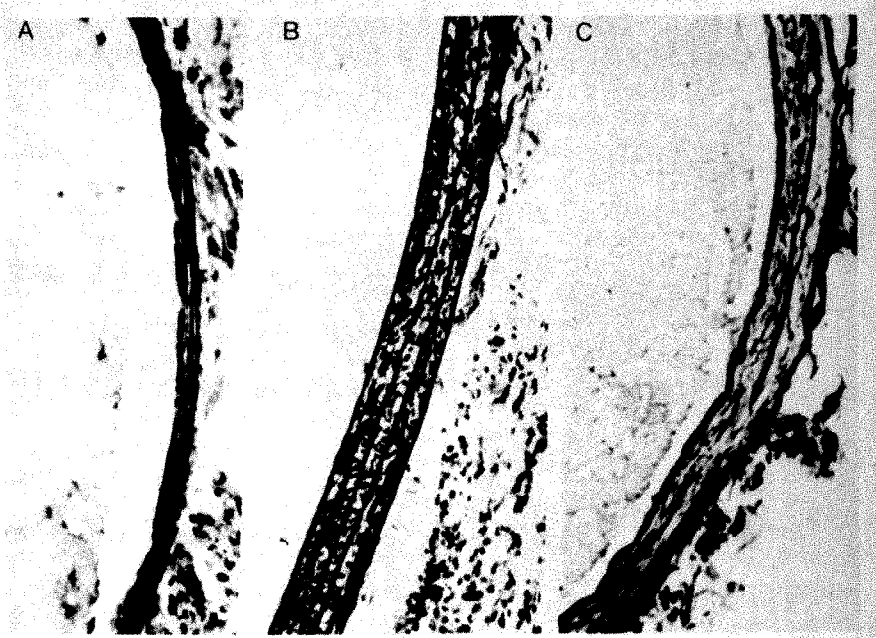

FIGURE 7. Photomicrographs of the muscular wall of the axial pulmonary artery of the right middle lobe, half way between the hilum and the periphery: **A,** from a 4 month old control infant; **B,** from the patient with double-outlet right ventricle; and **C,** from the patient with the absent pulmonary valve syndrome (Case 3). In **B** and **C** the wall is thicker than in **A.** The elastic laminae are very thick in **B** but are unevenly thick and fragmented in **C.** (Elastic Van-Gieson stain; original magnification ×40, reduced 25%).

ries; however, this does not explain the abnormal distal branching pattern.

From our knowledge of the timing of embryonic events, it is possible to suggest how the abnormal hilar branching pattern may arise. Alignment of the conotruncus (infundibulum and great arteries) with the ventricles takes place from the 30th to the 38th days of gestation.[27–29] If this process is disturbed, one result can be tetralogy of Fallot, as in Cases 2 and 3, and another result can be D-transposition of the great arteries, as in Case 1. Normally, it is just before this time that the definitive pulmonary arteries and ducti arteriosi are formed, from the 25th to the 29th days of gestation.[30,31] Therefore, we think that the characteristic abnormalities of the absent pulmonary valve syndrome probably appear between the 25th and 38th days of gestation. It may well be significant that during the 6th embryonic week, the segmental branches of the pulmonary arteries are the most actively growing pulmonary vascular structures.[31,32] We speculate that the increased pulmonary blood flow and pulse pressure associated with an absent pulmonary valve and an absent ductus arteriosus may stimulate their proliferation.

The question arises of why nonvascular structures such as the bronchi are also abnormal in the absent pulmonary valve syndrome. A single intrauterine insult at or before this critical time (25th to 38th days of gestation) could affect both the developing heart and lung, or the abnormal pulmonary arteries may compress the developing bronchi at the hilum and more peripherally (Fig. 3). Depending on the degree of compression, this extrinsic pressure could interfere with the ability of the bronchial tree to sprout new distal branches.

Why is absence of the ductus arteriosus so often associated with an absent pulmonary valve? The size of the ductus arteriosus appears to depend on the amount of right-to-left shunting through it in utero. Predictably, stenosis or atresia of the pulmonary outflow tract in tetralogy of Fallot is associated with a small or absent ductus arteriosus. Similarly, among patients with the absent pulmonary valve syndrome, those with the most severe pulmonary regurgitation (such as that due to absence of the pulmonary valve leaflets, and minimal pulmonary annular and infundibular stenosis) are most likely to lack a ductus.

Why are the pulmonary artery and its branches so large in the absent pulmonary valve syndrome, particularly in cases of absent ductus? The answer appears to be that, in late gestation, the pulmonary arteries must contain per unit time the right ventricular portion of the venous return, the flow that would ordinarily have been shunted through the ductus to the aorta, and the regurgitant fraction necessitated by the pulmonary regurgitation. The histologic abnormalities of the pulmonary arteries may well be secondary to this disturbed intrauterine hemodynamic function, in particular the extreme excursions between systolic distention and diastolic collapse.

Postnatal changes: Although the reduced number of bronchial generations in Case 1 (Table II) suggests an intrauterine insult, the reduced number of alveoli in Case 2 (Table II) could reflect a postnatal disturbance. The normal number of huge alveoli in Case 3 (Table II) most likely indicates a postnatal abnormality, probably secondary to prolonged ventilator therapy.

The 2 respirator-dependent patients were the ones in whom we observed structural changes in the peripheral pulmonary arteries similar to those associated with severe chronic hypoxia both clinically[33] and experimentally,[34] that is, extension of muscle into normally nonmuscular arteries. It seems likely, particularly in the infant who died at 3 months (Case 3), that these occurred postnatally. The patient who died at 4 days had D-transposition of the great arteries and ventricular septal defect; therefore, the excessively high pulmonary blood flow may also have contributed to the structural

changes, hence their early appearance.

Surgical implications: The 3 patients discussed in this report all had respiratory difficulties from birth and represent the group of patients with absent pulmonary valve that is most severely affected.[10] At the other end of the spectrum are patients with few if any cardiorespiratory symptoms who undergo elective cardiac surgery later in childhood.[35–37] For infants with severe symptoms, various surgical procedures have been proposed. Litwin et al.[38] in 1973 recommended that surgery be carried out in stages. The 1st stage, performed during infancy, involves relief of compression of one of the mainstem bronchi, usually by interposing a conduit between the main pulmonary artery and the distal right pulmonary artery. At the 2nd stage, performed later in childhood, the initial conduit is replaced by a larger one and the intracardiac defect is repaired.

More recently, good results were reported[39] by relieving the bronchial compression and correcting the intracardiac defect in a 1-stage procedure. The 1 step surgical technique has the distinct advantage of leaving the patient with normal rather than increased pulmonary blood flow. The result should be less distention of the intrapulmonary arteries, thereby lessening compression of hilar and intrapulmonary bronchi. The inclusion of some sort of pulmonary valve (such as a dura mater monocusp) may be desirable in theory, but in practice needs further assessment. Bronchodilator therapy may be beneficial in infants with exceedingly severe compression of the intrapulmonary bronchi. However, in some infants the severity of the intrapulmonary bronchial compression perhaps precludes a successful result from either surgical or medical therapy.

Once having described abnormalities in the branching pattern of the hilar segmental arteries on the basis of postmortem angiography, it now remains to diagnose these abnormalities in routine cineangiocardiograms obtained at cardiac catheterization. In the future it will be useful to correlate the severity of the vascular abnormalities with the degree of functional impairment judged by criteria such as the need for assisted ventilation, recurrence of pulmonary infections, or relative lack of clinical disturbance. It will be important also to correlate these abnormal hilar branching patterns with responses to the various forms of medical and surgical therapy.

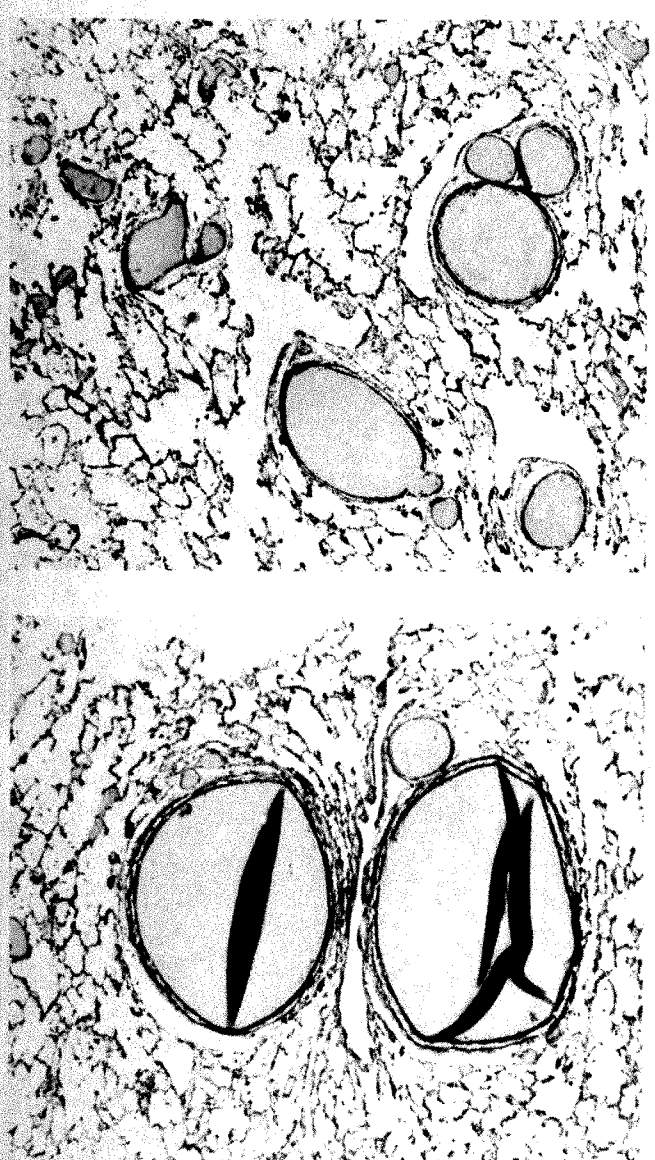

FIGURE 8. Top, photomicrograph of the intraacinar arteries in Case 2 showing slight increase in size but a normal number. Muscularity is appropriate in terms of both degree of extension into peripheral arteries and wall thickness. (Elastic Van-Gieson stain; original magnification ×100, reduced 29%). **Bottom,** photomicrograph of an intrapulmonary bronchus compressed between dilated preacinar arteries. (Elastic Van-Gieson stain; original magnification ×100, reduced 35%).

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Two-Dimensional Echocardiographic Identification of Pulmonary Artery Branch Stenosis

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Pulmonary artery branch stenosis is a not uncommon congenital lesion, noted in approximately 4% of children at the time of cardiac catheterization. Real-time 2-dimensional echocardiography was used to examine 10 patients with angiographically documented pulmonary branch stenosis. Five cases of pulmonary artery branch narrowing were identified by echocardiography without prior knowledge of angiographic findings. In 5 other patients whose angiographic results were known, the narrowings were identified in 4 of 5 cases. These results demonstrate the feasibility of evaluating pulmonary branch stenosis with the nonionizing, noninvasive method of 2-dimensional echocardiography.

Pulmonary artery branch stenosis is a congenital cardiac lesion that may occur alone or in combination with other cardiac anomalies, most commonly pulmonic valve stenosis, atrial and ventricular septal defects, and patent ductus arteriosus. Also, pulmonary artery stenosis is associated with the congenital syndrome of supravalvular aortic stenosis (Williams syndrome). Usually no cause of pulmonary artery branch stenosis is identified, but an association with maternal rubella syndrome has been recognized.[1] The diagnosis may be suspected clinically on the basis of a systolic murmur with wide radiation, but requires cardiac catheterization and angiography for confirmation. In this study we report the detection of these lesions using real-time 2-dimensional echocardiography, an application of echocardiography that has not previously been described to our knowledge.

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Methods

Study patients: The study group consisted of 10 patients, aged 5 to 25 years (Table I). Five of the patients (Cases 1 to 5) were studied either before angiography or without knowledge of angiographic results. The remaining 5 patients (Cases 6 to 10) were known to have angiographically documented peripheral pulmonary artery stenosis before echocardiographic study. Associated lesions included atrial septal defect in 2 patients, 1 of whom also had pulmonary valve stenosis; tetralogy of Fallot in 2 patients; and tricuspid atresia, single ventricle, and pulmonary atresia each in 1 patient. Three patients had no associated cardiac anomalies. Pressure data were available in 4 patients (Cases 6 to 9), and the peak systolic gradient across the stenosed pulmonary artery ranged from 19 to 81 mm Hg. In the remaining patients the pressures were not obtained because of severe stenosis or atresia (Cases 1 and 4), stenosis too distal (Case 10), or other anatomic anomalies (Cases 2, 3, and 5). A second group of 10 pediatric patients with angiographically documented normal pulmonary arteries was studied by echocardiography without knowledge of angiographic results.

Echocardiography: All patients were examined using real-time 2-dimensional echocardiography with a 90°, 3 MHz mechanical sector scanner (Advanced Technology Laboratories). All examinations were performed using parasternal, subcostal, and suprasternal/supraclavicular techniques.

Parasternal technique: The pulmonary valve is identified in the standard manner[2] and then the transducer is angled further to the left to attempt to visualize the main pulmonary

TABLE I Pulmonary Artery Findings

Case	Age (yr)	Echocardiogram	Angiogram	Associated Lesions
1	25	Miniscule RPA	Same as echo	Tricuspid atresia, PDA
2	7	Tubular narrowing of RPA, narrowed proximal PA	Same as echo	Pulmonary atresia, hypoplastic RV s/p Waterston shunt
3	11	Small RPA and MPA	Same as echo	Single ventricle s/p Waterston shunt
4	21	Absent RPA	Same as echo	Tetralogy of Fallot
5	11	Narrowed MPA and RPA	Same as echo	Tetralogy of Fallot s/p Blalock procedure
6	8	Narrowed RPA with small superior branch; narrowed LPA at origin	Same as echo	None
7	20	Narrowed RPA with post-stenotic dilatation; dilated MPA	Same as echo; also stenosis of LPA at origin of lingular branch	None
8	5	Narrowed LPA, dilated MPA	Same as echo	ASD
9	17	Narrowed distal RPA; dilated MPA with increased pulsations	Same as echo; narrowed LPA distally; multiple stenoses of 2° and 3° branches of RPA and LPA	Pulmonary valve stenosis; ASD
10	10	No abnormality seen	Narrowed RPA after superior branch take-off; superior branch ends in stump	None

ASD = atrial septal defect; Echo = echocardiogram; LPA = left pulmonary artery; MPA = pulmonary artery; PDA = patent ductus arteriosus; RPA = right pulmonary artery; RV = right ventricle; s/p = status post; VSD = ventricular septal defect.

trunk. In some patients minimal adjustment of the transducer brings the proximal portions of the right and left pulmonary artery into the echo plane (Fig. 1).

Subcostal technique: The pulmonary trunk and proximal portions of the primary branches are imaged in some patients, especially children, by placing the transducer in the subcostal area and directing it superiorly (Fig. 2).

Suprasternal/supraclavicular technique: The transducer is placed in the suprasternal notch and angled inferiorly and somewhat to the right to visualize a large segment of the right pulmonary artery (Fig. 3). In some patients the proximal portion of the superior branch of the right pulmonary artery is also seen before the vessel is lost within lung parenchyma. The transducer can then be directed somewhat posteriorly to visualize the left pulmonary artery. Although the left pulmonary artery is generally less easily visualized than the right pulmonary artery, the first portion of its branches is occasionally seen (Fig. 4).

Some of the pulmonary artery anatomy viewed in the foregoing approaches has been previously described and validated.[3,4] In our laboratory echocardiographic contrast studies utilizing injections of 5% dextrose have been performed during cardiac catheterization procedures in patients without pulmonary branch stenosis to validate pulmonary artery anatomy (Fig. 2 and 3).

Normal 2-dimensional echocardiographic dimensions have not been established for the pulmonary vessels. For the purposes of the study we considered stenosis present if (1) a vessel abruptly narrowed by 50% or more of its adjacent diameter, and (2) the right pulmonary artery was 25% or less of the transverse aortic arch diameter. The main pulmonary artery was considered dilated if its diameter measured in the precordial view was 1.5 or more times the diameter of the aortic root.

Results

Pulmonary artery echocardiographic findings (Table I, Fig. 5 to 7): The echocardiographic diagnosis of pulmonary branch artery stenosis was made prospectively in 5 patients (Cases 1 to 5) who were studied as part of routine noninvasive evaluation or follow-up of complex cardiac anomalies. In each case, cardiac angiograms confirmed the suspected stenosis. The remaining 5 patients (Cases 6 to 10) were studied knowing that pulmonary artery stenosis was present. In general, these patients had fewer associated cardiac anomalies, and 3 were being followed up only for isolated pulmonary branch stenosis. In all but 1 (Case 10), stenotic regions were identified by echocardiography,

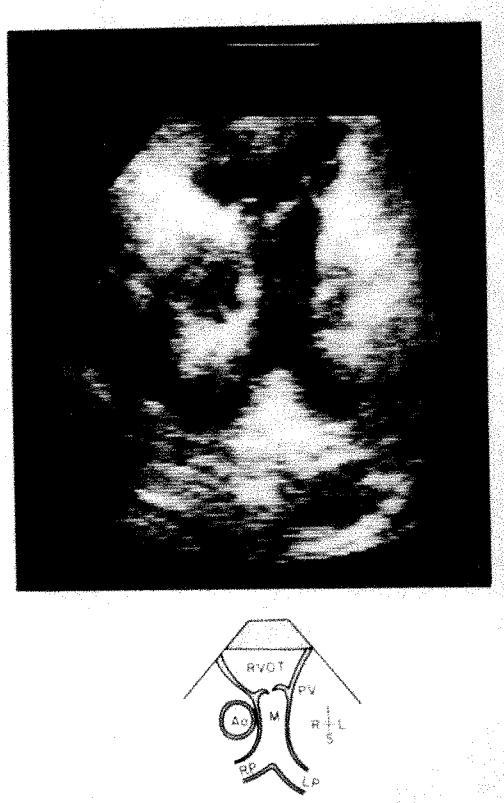
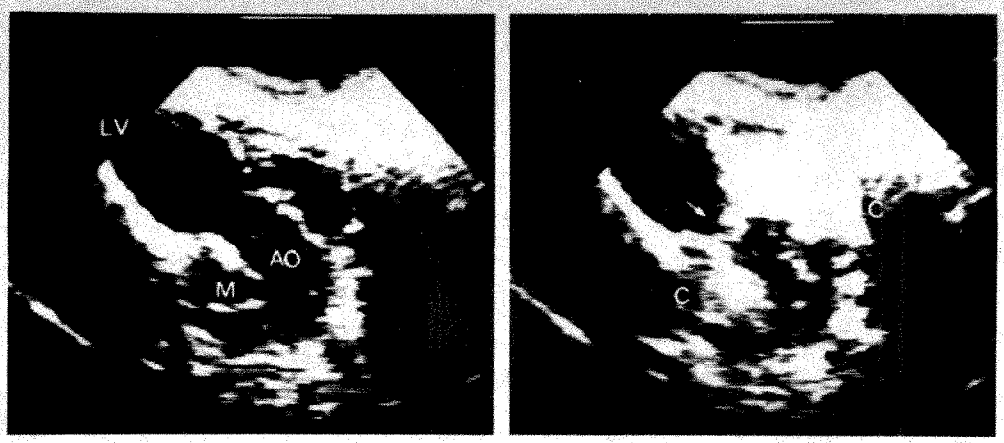


FIGURE 1. Pulmonary trunk and primary branches from parasternal transducer position. Diagrammed below are the right ventricular outflow tract (RVOT), pulmonary valve (PV), main pulmonary artery (M), right pulmonary artery (RP), and left pulmonary artery (LP). AO = aorta; I = inferior; L = left; R = right; S = superior.



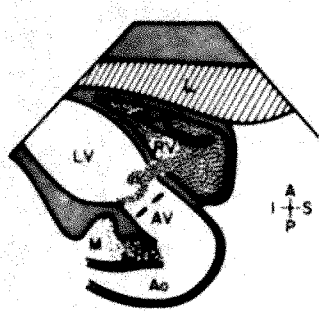
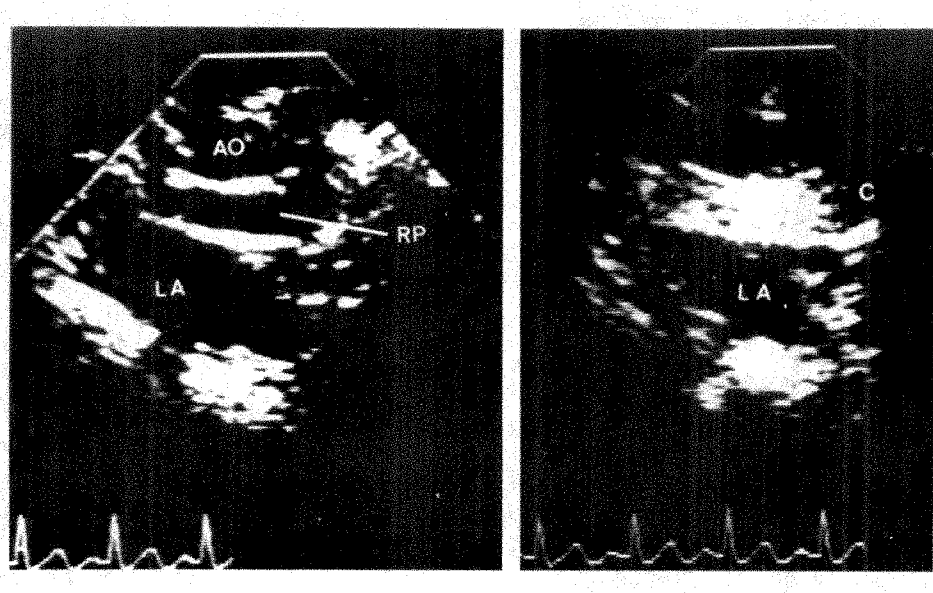


FIGURE 2. Pulmonary artery visualization from subcostal transducer position. **Top left,** the main pulmonary artery (M) and the proximal portion of its right branch are visualized in a patient with a ventricular septal defect and a right-to-left shunt. **Top right,** contrast injections into the inferior vena cava result in contrast filling (C) of the right ventricle (RV) and main and right pulmonary arteries. Some contrast medium (**arrow**) passes into the left ventricle (LV) through the ventricular septal defect. In the diagram at **left,** A = anterior; Ao = aorta; AV = aortic valve; I = inferior; L = liver; P = posterior; S = superior.



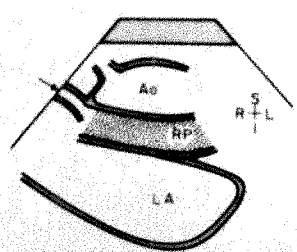
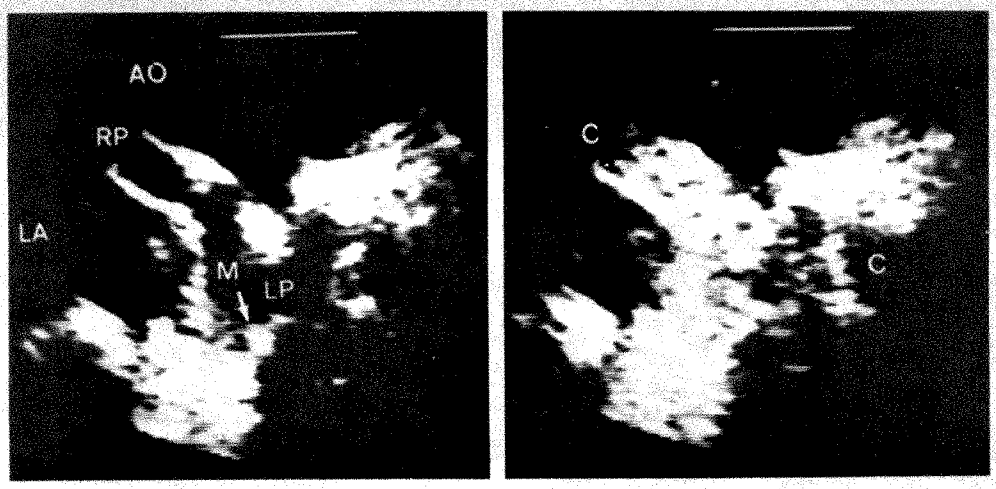


FIGURE 3. Right pulmonary artery from suprasternal transducer position. **Top left,** a large segment of the right pulmonary artery (RP) is seen between the transverse aorta (AO) and left atrium (LA). Note also the proximal portion of the superior branch of the right pulmonary artery (**arrow**). **Top right,** contrast medium (C) injected from the inferior vena cava fills the right pulmonary artery. At **left,** I = inferior; L = left; R = right; S = superior.



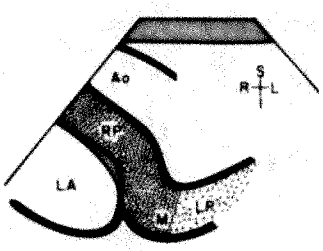
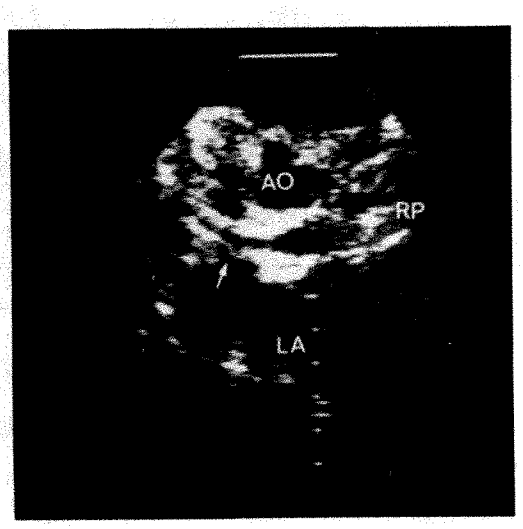


FIGURE 4. Pulmonary arteries from the suprasternal transducer position. The transducer is angled further leftward and somewhat posteriorly compared with the position in Figure 3. **Top left,** before injection of contrast medium the right pulmonary artery (RP) is seen located between aorta (AO) and left atrium. The anterior aortic wall is not visualized because of reduced gain in the proximal echo field used to optimize pulmonary artery recordings. The right branch is contiguous with the main pulmonary trunk (M) and left branch (LP). **Top right,** contrast medium (C) injected in the inferior vena cava appeared first in the main pulmonary artery and then quickly filled the branches. At **left,** I = inferior; L = left; R = right; S = superior.



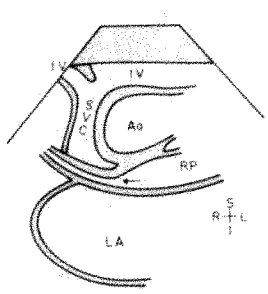
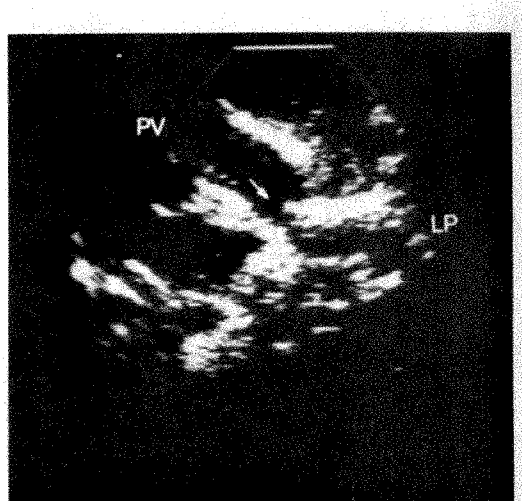


FIGURE 5. Case 2, suprasternal transducer position. The proximal right pulmonary artery (RP) is of normal caliber, but tapers distally to a segment of tubular narrowing (**arrow**). Ao = aorta; I = inferior; IV = innominate vein; L = left; LA = left atrium; R = right; S = superior; SVC = superior vena cava.



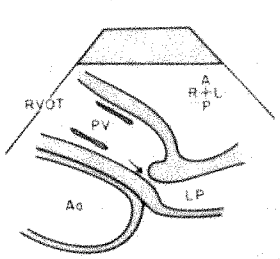


FIGURE 6. Case 6, parasternal transducer position. The left pulmonary artery (LP) is shown with narrowing at its take-off point from the main trunk (**arrow**). The right branch is not seen in this plane. A = anterior; Ao = aorta; L = left; P = posterior; PV = pulmonary valve; R = right; RVOT = right ventricular outflow tract.

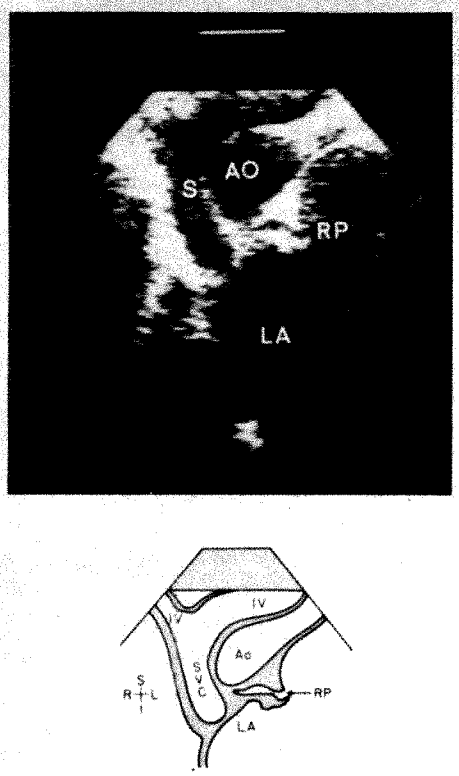


FIGURE 7. Case 1. Pulmonary artery branch stenosis associated with tricuspid atresia. The narrow space between the aorta (AO) and left atrium (LA) represents a miniscule right pulmonary artery (RP) seen from the suprasternal approach. I = inferior; IV = innominate vein; L = left; R = right; S = superior; S (SVC in diagram) = superior vena cava.

which corresponded closely to the angiographic findings. Although all transducer approaches were useful in recognizing the pulmonary arteries, the main pulmonary artery was most consistently imaged from the parasternal position, and the right and left pulmonary arteries with their proximal branches were seen best from the suprasternal/supraclavicular approach. The main pulmonary artery and proximal portions of its two branches were visualized in all patients utilizing multiple transducer positions.

Correlation with angiographic findings: In most cases the echocardiographic findings correlated well with those shown in the angiogram, especially when the stenosis was proximal. We failed to see stenosis of the lingular branch of the left pulmonary artery in 1 patient (Case 7), bilateral multiple narrowings of secondary and tertiary branches of the pulmonary artery in 1 patient (Case 9), and narrowing of the right pulmonary artery distal to the origin of the superior branch in a third patient (Case 10). The interesting finding of a dilated main pulmonary artery with prominent pulsations was noted in Patient 9 with the multiple stenoses of the secondary and tertiary pulmonary branches. In 2 patients (Cases 1 and 4) the right pulmonary artery was miniscule or absent, and these findings were confirmed by angiography in both. In the 10 patients with angiographically normal pulmonary arteries, no evidence of narrowing in the pulmonary vascular tree was detected by echocardiography.

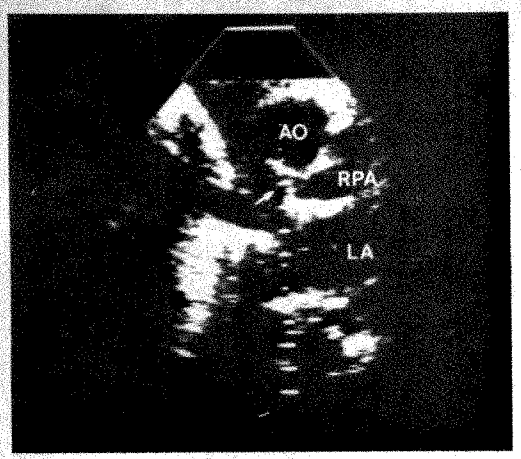
Discussion

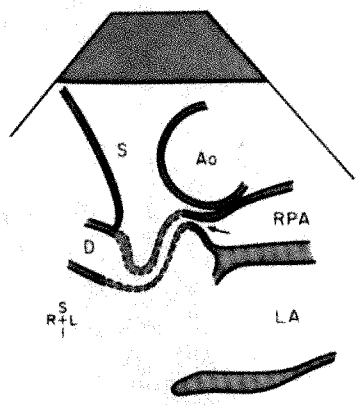
Clinical features: Stenosis of the pulmonary artery has been recognized with increasing frequency since cardiac catheterization and angiography became available. Several classifications have been suggested based on anatomic location (trunk, right or left branches, peripheral branches) and type of stenosis (tubular, discrete).[5,6] It is a relatively common congenital lesion, being reported in 4% of children undergoing catheterization.[7] Approximately half of the patients with pulmonary artery stenosis have associated cardiac lesions, most commonly pulmonic valve stenosis, atrial septal defect, ventricular septal defect, patent ductus arteriosus, or tetralogy of Fallot.[8]

A systolic murmur, typically grade 2/6 to 3/6 with wide radiation to the back and axillae, is almost always present but can be obscured by other cardiac anomalies.[9] The natural history of isolated pulmonary artery stenosis is generally benign,[10] but complications including pulmonary hypertension, right ventricular failure, pulmonary artery thrombosis, and poststenotic aneurysmal dilatation with rupture and hemoptysis have been reported.[8,11] A number of investigators have pointed out the importance of defining pulmonary artery anatomy before surgical repair of complicated cardiac anomalies such as tetralogy of Fallot. Unrecognized pulmonary branch stenosis has led to poor postoperative results because of unrelieved pulmonary hypertension.[12] Surgical correction of pulmonary artery stenosis has been described and is feasible if the obstruction occurs proximally.[13]

Echocardiographic diagnosis: This is the first study demonstrating the feasibility of diagnosing pulmonary artery branch stenosis utilizing real-time 2-dimensional echocardiography. Previously, confirmation of clinically suspected pulmonary artery stenosis required cardiac catheterization and angiography. Both M-mode and 2-dimensional echocardiography have previously been applied to the diagnosis of Williams syndrome. One report describes M-mode identification of supravalvular aortic stenosis in a patient also having multiple pulmonary branch stenosis, but no attempt was made to visualize the pulmonary stenoses.[14] A recent report[15] described the 2-dimensional echocardiographic features of aortic stenosis in a patient with Williams syndrome, but pulmonary artery stenosis was angiographically absent.

In our series, abnormalities of the pulmonary artery were detected by echocardiography prospectively in 5 patients and 4 of 5 patients with known pulmonary branch stenosis. The lesions which were missed occurred peripherally in close vicinity to the lung, which may have obscured the more distal pulmonary branches. This constitutes the major limitation of the technique since only the main pulmonary artery, right pulmonary artery, left pulmonary artery, and occasionally their first branches can be viewed before being obscured by lung





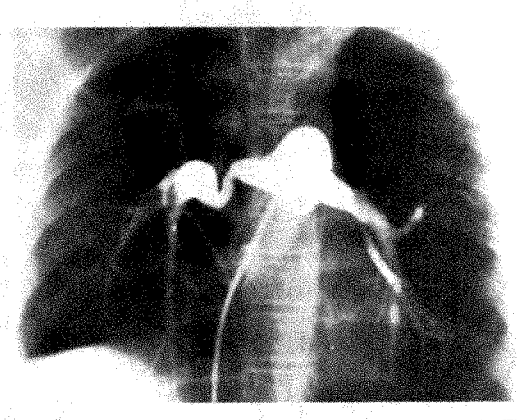
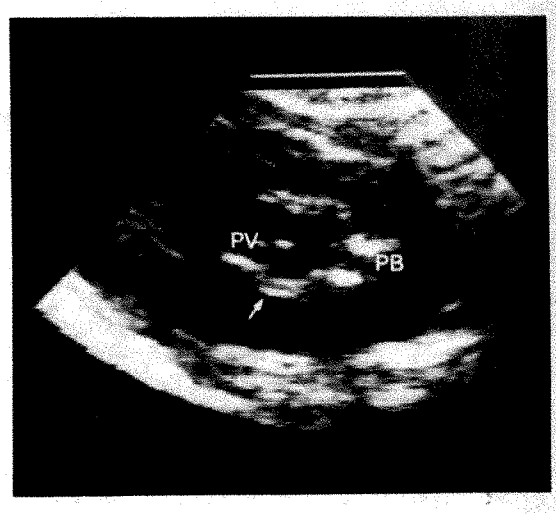


FIGURE 8. Case 7. **Top and middle,** suprasternal approach. The right pulmonary artery (RPA) lying between aorta (AO) and left atrium (LA) abruptly narrows (**arrow**). It is then lost as it courses out of the 2-dimensional echo plane. Where it reappears distally, the lumen is wide without evidence of stenosis. The schematic drawing shows the tortuous segment of the right pulmonary artery (**dashed line**) which was not visualized on the echocardiogram and which connects the area of stenosis (**arrow**) and the poststenotic dilatation (D). (S = superior vena cava. Orientation: I = inferior, L = left, R = right, S = superior). **Bottom,** the pulmonary artery angiogram shows narrowing of the right pulmonary artery corresponding to the echocardiogram. Poststenotic dilatation seen on the angiogram corresponds to the area of distal luminal widening (D) seen on echocardiography. This illustrates a limitation of 2-dimensional echocardiography. The technique can only view, at any given time, structures or portions of structures located in the same echocardiographic plane.

parenchyma. Tertiary branch stenosis cannot be visualized by echocardiography.

The pulmonary valve and main pulmonary artery are best seen using the parasternal approach, and were visualized in all of our patients in this manner. The right and left branches can be seen in their proximal portions using either the precordial or subcostal view, but are best seen from the suprasternal approach. The left pulmonary artery is often less easily seen than the right pulmonary artery since it has a shorter course before reaching the lung hilum. The bifurcation of the main pulmonary artery into right and left branches is often well imaged from the parasternal position, but from the suprasternal view it may be difficult to distinguish the main pulmonary artery from the beginning of its branches. The angled 2-dimensional transducer head used in this study is well suited for suprasternal examination, but transducer size may be a limitation in smaller patients.

Clinical applications: This new application of 2-dimensional echocardiography is of clinical value in noninvasively confirming the diagnosis in patients who are suspected to have isolated pulmonary artery branch



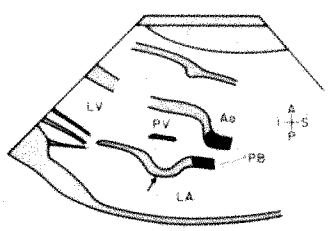


FIGURE 9. Pulmonary artery banding. Parasternal transducer position. This patient with transposition of the great vessels and ventricular septal defect has a pulmonary artery band (PB) surgically placed to narrow the pulmonary artery trunk and limit pulmonary blood flow. Note the bright echoes from the synthetic banding material, which help differentiate iatrogenic narrowing from congenital stenosis. The **arrow** indicates dilatation of the posterior pulmonic sinus which occurred secondary to the banding procedure. A = anterior; AO = aorta; I = inferior; LA = left atrium; LV = left ventricle; P = posterior; PV = pulmonary valve; S = superior.

stenosis, or in patients with complex cardiac lesions undergoing surgery in whom failure to recognize associated branch artery stenosis may lead to poor postoperative results. The technique may also be used to examine patients with maternal rubella syndrome, Williams syndrome, or other conditions which predispose to pulmonary branch stenosis. Although our series is too small to comment on the specificity or sensitivity of the test, we were able to prospectively identify five cases of pulmonary artery branch stenosis by echocardiography. We now routinely look at pulmonary artery structure during echocardiographic examinations. A review of 10 sequential pediatric patients with normal pulmonary artery angiograms who underwent echocardiography blinded to angiographic results showed no echocardiographic false-positive diagnoses for pulmonary artery stenosis.

Technical considerations: Some pitfalls and problems in the diagnosis of branch pulmonary artery stenosis by echocardiography need be considered. A physiologic peripheral pulmonary branch stenosis may be seen in neonates, usually preterm infants, in whom the branch arteries are considerably smaller in diameter relative to the diameter of the main pulmonary artery than they are several months later. In neonates, the diagnosis of true structural bilateral stenosis should be made with caution only after serial examinations. In our series the youngest patient was 5 years old, so this problem did not arise. Technical problems include difficulty in accurate assessment of vessel diameter. The transducer should be moved and angled in multiple directions to obtain maximal vessel diameter. The vessel size may be underestimated if the echo plane does not transect the middle of the vessel when viewed in long axis. Vessel tortuosity may prevent visualization of its full length in a given 2-dimensional plane (Fig. 8). The echo plane is equivalent to a thin cross-sectional slice through the heart and great vessels, and multiple 2-dimensional views may be required to piece together an overall picture of vessel anatomy. Narrowing of the main pulmonary artery by surgical banding may be confused with congenital stenosis. However, the synthetic banding material produces dense bright echoes in the region of the banded area, and this finding is helpful in differentiating it from congenital pulmonary artery stenosis (Fig. 9). As with other echocardiographic examinations, it is important to utilize mutliple depth and gain control settings to obtain optimal images of the pulmonary arteries.

Conclusion: Our findings demonstrate the capability of detecting branch pulmonary artery stenosis using real-time 2-dimensional echocardiography. The parasternal and subcostal views are useful for imaging the main pulmonary artery. With the suprasternal/supraclavicular approach, longer segments of the right and left pulmonary arteries as well as the proximal secondary branches can be visualized. More peripheral branches cannot be seen with echocardiography. These results are preliminary but suggest that this nonionizing, noninvasive technique deserves further prospective investigation in the evaluation of pulmonary branch stenosis.

Acknowledgment

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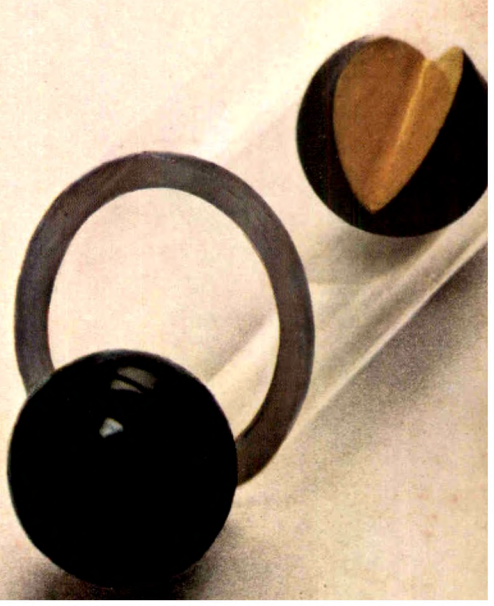

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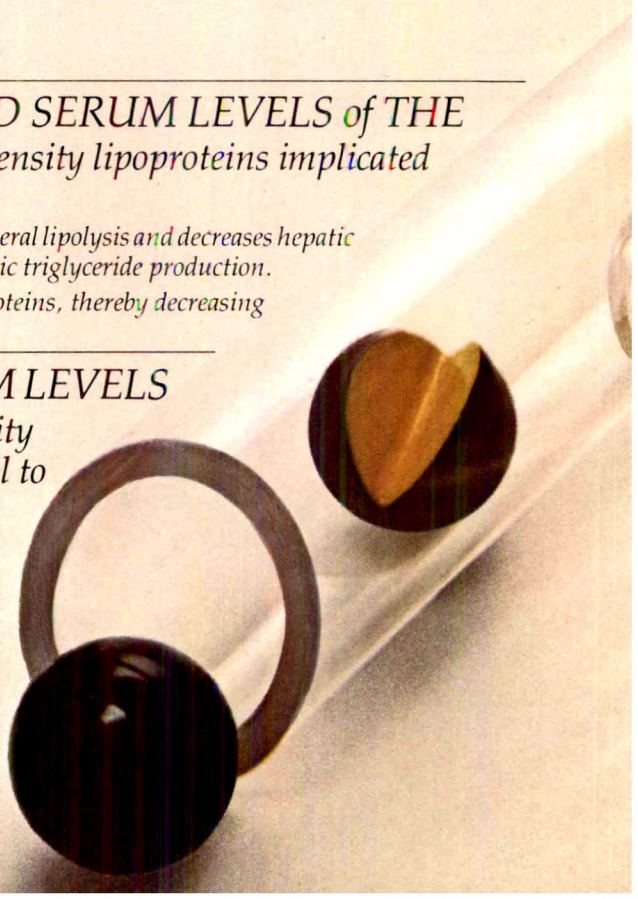

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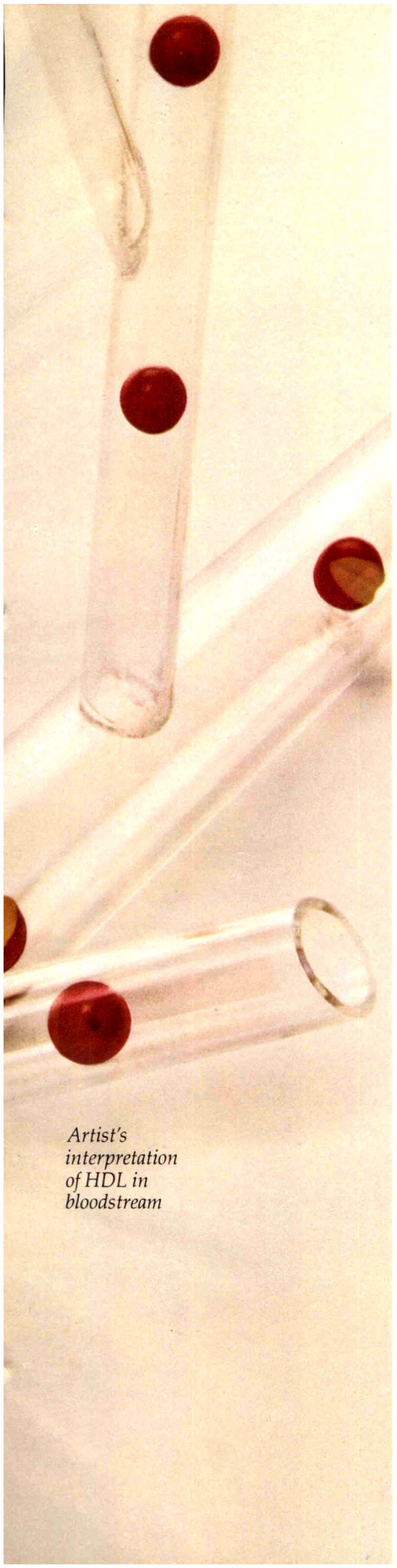

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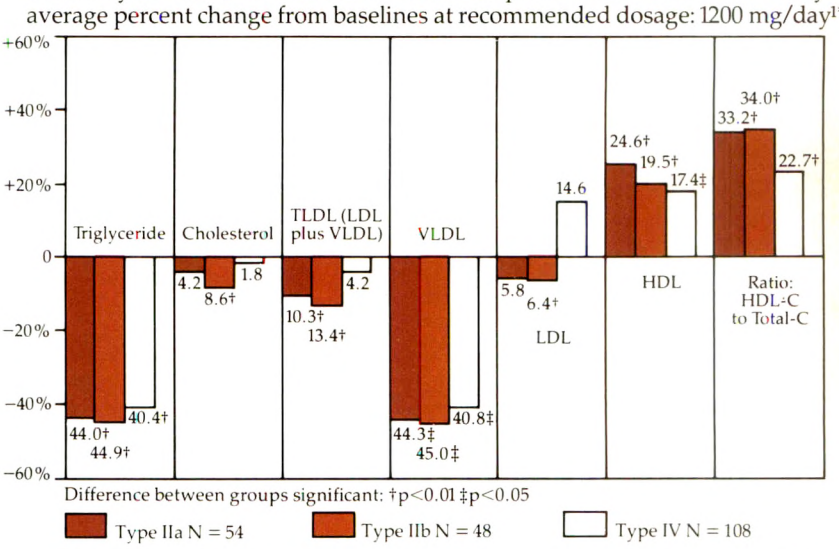

Difference between groups significant: †$p<0.01$ ‡$p<0.05$

Type IIa N = 54 Type IIb N = 48 Type IV N = 108

*Data cited on this graph reflect clinical experience based on the multicenter trial. It does not imply an indication for types IIa and IIb dyslipidemias.

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Liver Function	529	None
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Ophthalmologic	551	None
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The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID also inhibits synthesis of VLDL carrier apoprotein, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following single doses and 1.3 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine primarily as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO
		Total	VLDL	LDL	HDL	HDL Cholesterol / Total Cholesterol
IIa	−44%	−4.2%	−44.3%	−5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	−6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure.

Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk.

LOPID (gemfibrozil) has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. However, it must be understood that there is no evidence that use of any lipid-altering drug will be beneficial in preventing death from coronary heart disease (See WARNINGS). Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of drug-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings)

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies: Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis — LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants — Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. *Initial Therapy* — Before instituting LOPID (gemfibrozil) therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. *Continued Therapy* — Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. *Seasonal Variation of Lipid Levels* — LOPID is not expected to alter seasonal variations of higher serum lipid values in midwinter and late summer or the lower values in fall and spring.

4. *Impairment of Fertility* — Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

5. *Pregnancy Category B* — Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 5.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. *Nursing Mothers* — Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. *Hematologic Changes* — Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

8. *Liver Function* — Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

9. *Cardiac Arrhythmias* — Although no clinically significant abnormalities occurred that could be attributed to LOPID, the possibility exists that such abnormalities may occur.

10. *Use in Children* — Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria

Central Nervous System: headache, dizziness, blurred vision

Musculoskeletal: painful extremities

Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:

Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia

Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints

Central Nervous System: vertigo, insomnia, paresthesia, tinnitus

Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)

Miscellaneous: fatigue, malaise, syncope

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID (GEMFIBROZIL). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

0669G010

References: 1. Data on file, Medical Affairs Dept, Parke-Davis.

PARKE-DAVIS
Warner-Lambert Company
Morris Plains, NJ 07950

WARNER LAMBERT

PD-56-JA-0550-P-1(2-82)

EXPERIMENTAL STUDIES

Ventricular Performance and Biochemical Alteration of Regional Ischemic Myocardium After Reperfusion in the Pig

MARVIN L. MURPHY, MD, CHUN FU PENG, PhD, JAMES J. KANE, Jr., MD, and KARL D. STRAUB, MD, PhD

Reperfusion of acutely ischemic myocardium may cause profound alterations in left ventricular wall performance and metabolism. This study evaluates regional left ventricular wall thickness, analyzes metabolic and biochemical alterations, and examines tissue hemorrhage during 15, 30, and 120 minutes of myocardial ischemia, each followed by 120 minutes of reperfusion. Reperfusion after 15 minutes of ischemia showed nearly normal ventricular wall thickening and motion, intact metabolic and biochemical function, and no tissue hemorrhage. However, reperfusion after 30 and 120 minutes of ischemia was associated with ventricular wall thickening and failure to resume systolic and diastolic wall motion. Furthermore, adverse metabolic and biochemical alterations and reperfusion zone hemorrhaging increased proportionally with the duration of ischemia. These findings suggest critical myocardial damage occurring between 15 and 30 minutes of ischemia in an animal model without preexisting coronary collateral circulation. The observed metabolic and biochemical changes are consistent with irreversible cell membrane defects, allowing calcium ion accumulation and thus adversely affecting diastolic relaxation and systolic thickening.

Saphenous vein bypass grafting is accepted therapy for chronic, stable angina unresponsive to medical treatment, but its use in acute myocardial infarction remains controversial. In addition, current interest in the use of thrombolytic agents in acute infarction focuses renewed attention on the functional and metabolic aspects of reperfusion of ischemic myocardium.[1–5] Experimental studies show that reperfusion of acutely ischemic myocardium may be deleterious,[6] resulting in myocardial necrosis[7] as well as striking changes in left ventricular wall thickness and contractility.[8,9] The mechanism of reperfusion damage is not well understood and may relate to the duration and degree of ischemia. Changes in regional blood flow and reactive hyperemia have been suggested as an explanation for injury.[10,11] Other observers[12] note considerable edema in reperfused tissue and suggest that both edema and loss of cell volume regulation play an important role in the development of irreversible ischemic injury. A recent extensive review[13,14] of factors affecting infarct size emphasizes the complexity of data interpretation in human and experimental reports of ischemia and reperfusion.

The purpose of this study was (1) to define the magnitude and time course of changes in left ventricular performance by evaluating wall thickening and thinning, as related to varying periods of coronary occlusion followed by a standard reperfusion time, and (2) to relate changes in left ventricular wall motion to the accompanying metabolic state of the myocardium.

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Methods

Experimental protocol: The pig was chosen as the experimental model because its major coronary distribution, collateral circulation, and conduction system blood supply is identical to that of man.[15–17] Twenty-three mature farm pigs

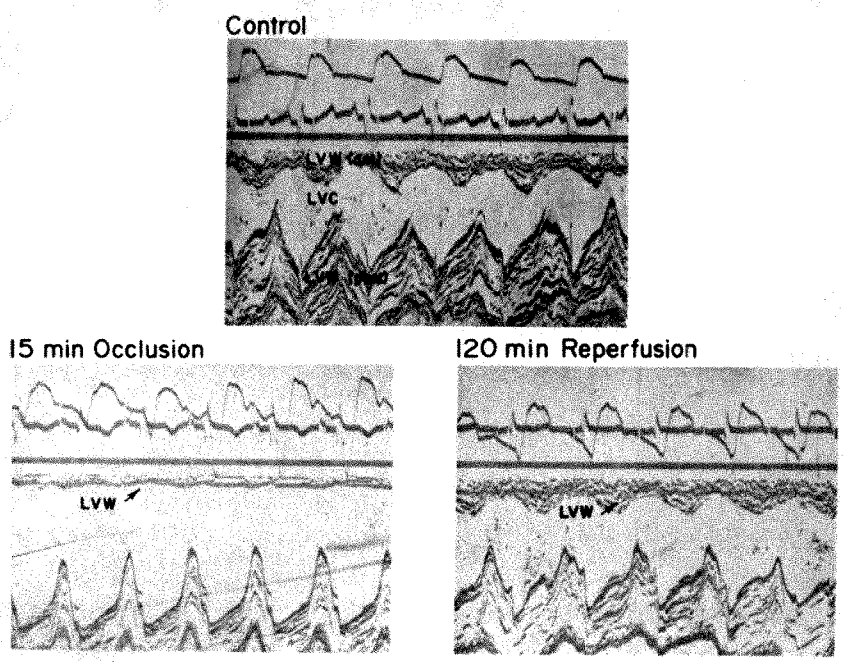

FIGURE 1. Echocardiographic left ventricular wall thickness. **Top panel,** control echocardiogram recorded before coronary occlusion. The anterior (ant) left ventricular wall (LVW) thickens during systole followed by diastolic thinning. **Lower left,** recording performed over the same area of the left ventricle after 15 minutes of coronary occlusion. There is loss of systolic thickening and thinning of the anterior wall. **Lower right,** after 120 minutes of reperfusion, there is near-normal left ventricle thickening and thinning. LVC = left ventricular chamber; LVW = left ventricular wall; post = posterior.

weighing 30 to 55 kg were anesthetized with 6% phenobarbital sodium administered intravenously after an 18 hour fast. Tracheostomy was performed and respiration maintained with a Harvard pump respirator, using room air supplemented by oxygen and adjusted to maintain an arterial PaO_2 greater than 100 mm Hg and a pH of 7.4. A midline sternal splitting thoracotomy was made and the heart suspended in a pericardial cradle exposing the distribution of the left anterior descending coronary artery. Aortic pressure, left ventricular pressure, and lead II of the electrocardiogram were continuously monitored.

The left anterior descending coronary artery was reversibly occluded just distal to the 1st or 2nd diagonal branch using a nontraumatic rubber ligature producing an area of ischemia approximately 25 to 30% of the total left ventricular mass. In 7 animals the ligature was applied for 15 minutes and then released with reperfusion of the ischemic zone carried out for an additional 120 minutes. A 2nd group of 8 animals had coronary occlusion for 30 minutes followed by reperfusion for 120 minutes. A 3rd group of 8 animals had coronary occlusion for 120 minutes followed by reperfusion for 120 minutes. The coronary vein was preserved in each case to allow venous washout during reperfusion.

Ventricular arrhythmia during occlusion was treated with minimal effective doses of lidocaine or, in the case of ventricular fibrillation, with electric countershock. At the end of reperfusion, 2.5 cc of 10% alphazurine 2-G blue dye was injected in a systemic vein to identify areas of the myocardium not well perfused. This dye stains perfused and presumably viable tissue a vivid blue but does not stain ischemic or nonperfused tissue[18] and has no effect on mitochondrial function or sarcoplasmic reticulum calcium transport. Immediately after injection of the dye, the heart was removed and taken to a cold room where samples were excised from uninvolved and reperfused areas of the left ventricle using surface anatomy and dye staining as guidelines. The posterior aspect of uninvolved left ventricle was used for sampling and was considered as a control for metabolic studies.

Echocardiographic methods: Left ventricular wall thickness was measured serially before and after occlusion by placing a 5.0 MHz nonfocused ultrasound transducer directly over the involved left ventricle. The transducer was coupled to an Echoline 20A ultrasonoscope (Smith Kline and French) with data being recorded on a strip chart recorder (Honeywell). To avoid pressure artifact and distortion of the heart wall, the transducer was held very lightly in contact with the epicardial surface over the center of the involved area of left ventricle, using the coronary artery surface anatomy as a landmark. The ischemic area was easily identified by the dark coloration and verified by S-T segment elevation on the epicardial electrode mapping over the involved area. This hand-held method resulted in reproducible echocardiographic data by assuring perpendicular orientation of the transducer with respect to the epicardial surface. Wall thickness was measured in millimeters at midsystole and end-diastole, with each final measurement being the mean of 5 consecutive cardiac cycles. The transducer itself caused a 3 mm layer visible as a dark stripe at the top of the echocardiograph. This thickness was subtracted from the total thickness for purposes of calculation.

Metabolic procedures: Tissue samples from control and reperfused left ventricles were homogenized with a Polytron PT-10 homogenizer at low speed in a medium containing 0.25 *M* sucrose and 20 m*M* Tris buffer (pH 7.5). Mitochondria were isolated by a method previously described.[19] After the final washing, mitochondria were suspended in a medium containing 0.1 m*M* Hepes potassium (N-2-hydroxyethylpiperazine-N′-2-ethanesulfonic acid) buffer (pH 7.4), with 250 m*M* sucrose. Mitochondria from ischemic, reperfused myocardium are very fragile.[20] The yield of mitochondrial protein measured by total protein content from ischemic, reperfused myocardium is much lower than that from nonischemic tissue. Mitochondrial protein was determined by the Biuret method.[21] Incubation mixtures contained 20 m*M* Tris buffer (pH 7.4), 100 m*M* sucrose, 100 m*M* potassium chloride, 5 m*M* inorganic phosphate, and 10 m*M* of either glutamate or malate plus pyruvate as substrate. Oxygen uptake was determined polarographically with a Clark electrode.[22] Adenosine diphosphate (ADP), 300 nmol, was added to the reaction mixture to initiate mitochondrial respiration. All reactions were carried out at 30°C. Uptake of calcium by mitochondria was monitored with the use of an oxygen electrode and a sensitive re-

cording pH electrode, as previously described.[23] Calcium uptake was also determined with $^{45}Ca^{2+}$ at a designated time after the addition of $^{45}CaCl_2$ by rapidly filtering the incubation mixture through a millipore filter.[24] The radioactivity of $^{45}Ca^{2+}$ of each sample was determined with a liquid scintillation spectrometer (Beckman). Sarcoplasmic reticulum vesicles were isolated from control and ischemic myocardium using the method described by Harigaya and Schwartz.[25] The kinetic features of calcium uptake by sarcoplasmic reticulum vesicle were determined with the use of murexide and dual wave-length spectrophotometry for measurement. The extent of calcium uptake by sarcoplasmic reticulum vesicles was studied by the use of radioactive $^{45}Ca^{2+}$ in the presence of oxalate.[24]

Tissue adenosine triphosphate (ATP) content was determined on duplicate tissue samples obtained by plunge biopsy using a renal biopsy needle (Travenol) just before sacrificing the animal. The needle was cooled in liquid nitrogen, plunged into the heart to obtain tissue, and immediately returned to a vial containing liquid nitrogen. Tissue for ATP determination was thus removed and frozen within 3 to 5 seconds. These samples were extracted in boiling water and ATP content was determined by firefly luciferase reaction.[26]

Samples from control and reperfused left ventricles were also taken for histologic section and examined by light microscopy for hemorrhage, with the degree of hemorrhage on each section being scored subjectively as none, slight, moderate, or severe. Water content of control and reperfused tissue samples was determined by weighing samples before and after 24 hours of dessication in a freeze-dryer (Virtis model 10-147 MRBA).

Tissue and mitochondrial samples for calcium content were extracted by a glacial acetic acid-trichloroacetic acid mixture,[27] and total calcium content was determined with an atomic absorption spectrophotometer with calcium carbonate as the standard.[28]

Data are presented as mean ± standard deviation and analyzed using Student's paired *t* test.

Results

Gross and microscopic findings: Within 1 to 2 minutes of coronary occlusion and ischemia the involved segment of left ventricle in all three groups of animals demonstrated cyanosis, flattened veins and arteries, and paradoxic systolic bulging, which persisted throughout occlusion. On reperfusion the coronary arteries and veins of the involved segment became distended and myocardial color was restored. The involved segment from 30 and 120 minute groups became firm to palpation compared with uninvolved areas of left ventricle on reperfusion. This effect was subjectively less evident in the 15 minute group and improved with time. When samples were taken from the left ventricle at the end of each experiment, reperfused areas of 30 and 120 minute groups had a firm texture compared with the near-normal tone of the 15 minute group and with the soft pliable uninvolved myocardium.

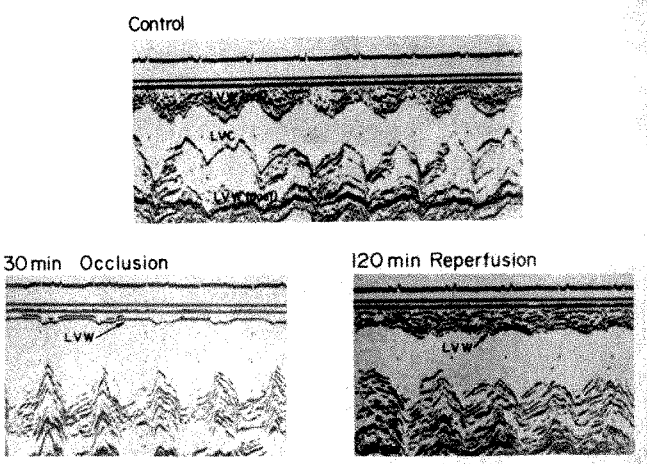

FIGURE 2. The panel arrangements are identical to those in Figure 1, but the occlusion time is 30 minutes. Note marked diastolic thickening of the anterior left ventricular wall (LVW) with minimal systolic thickening after reperfusion.

Review of microscopic sections showed no hemorrhage in areas of control left ventricle from the 15, 30, or 120 minute ischemia groups; no hemorrhage in reperfused areas of the 15 minute ischemic group; slight hemorrhage in reperfused areas of the 30 minute ischemic animals; and severe hemorrhage in sections of reperfused tissue from the 120 minute ischemia group.

Left ventricular wall thickness: Thinning of the ischemic myocardium occurred promptly and persisted

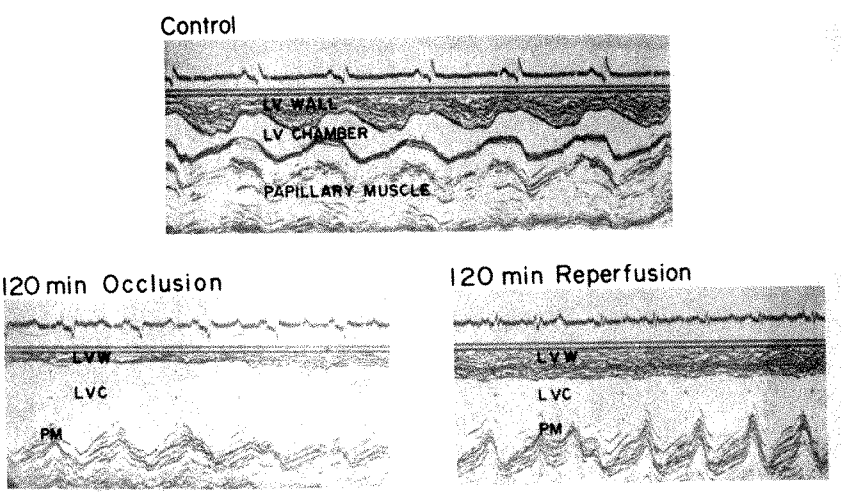

FIGURE 3. The panel arrangements are identical to those in Figure 1, but the occlusion time is 120 minutes. Note the marked thickening of the anterior left ventricular wall (LVW) with no wall motion. PM = papillary muscle.

throughout occlusion. This thinning was accompanied by systolic expansion of the ischemic area, which was also maintained until reperfusion. Representative echocardiographic changes in wall thickness at the center of the ischemic area for 1 animal in each of the 15, 30, and 120 minute groups are shown in Figures 1 to 3. During the control period in each illustration (top panel), the anterior myocardial thickening illustrates normal systolic wall motion. During occlusion of 15, 30, or 120 minutes (bottom left panel), there is loss of contraction and diastolic and systolic wall thinning. After reperfusion (bottom right panel) there is systolic thickening and diastolic thinning, comparing favorably with the control in the 15 minute ischemia group. After reperfusion in the 30 minute group, the anterior wall is thickened and there is minimal systolic thickening. In the 120 minute group prominent thickening of the anterior myocardial wall is seen without systolic or diastolic motion.

The variability of thickening of the ischemic left ventricle after reperfusion is illustrated for all animals in the 3 groups (Fig. 4 to 6). Control values are comparable for all groups. In the 15 minute ischemia group during reperfusion (Fig. 4), systolic anterior wall thickening improves gradually, ultimately approaching 75% of the control, and diastolic thinning is essentially normal. These findings contrast with the 30 (Fig. 5) and 120 minute ischemia (Fig. 6) groups in which effective systolic thickening and diastolic thinning are lost. The range of values is somewhat greater in the 30 minute group because of resumption of a measure of systolic thickening in 3 of 8 animals.

Metabolic data: Table I illustrates the results of oxidative phosphorylation for mitochondria prepared from control and reperfused tissue for the 15, 30, and 120 minute ischemia groups. Indexes of oxidative phosphorylation, including state 3 respiration (QO_2), ADP/O ratio, and respiratory control index (RCI), are shown. There was no significant difference for any of these variables for control tissue from the 15, 30, or 120 minute ischemia groups. In reperfused preparations, state 3 respiration, ADP/O ratio, and respiratory control index of mitochondria were slightly decreased in the 15 minute ischemia group. These variables were markedly decreased in the 30 and 120 minute ischemia groups compared with the 15 minute group ($p < 0.001$). These results suggest that mitochondria subjected to 15 minutes of ischemia and reperfusion were able to generate ATP with relatively normal efficiency. In contrast, oxidative phosphorylation was markedly impaired after 30 and 120 minutes of ischemia and reperfusion.

Figure 7 is a typical example of oxygen and pH electrode recording of Ca^{2+} uptake by mitochondria. The rate of Ca^{2+}-induced oxygen consumption and H^+ ejection by mitochondria is shown in each tracing. The rate of Ca^{2+} uptake was measured by the rate of H^+ ejection at the initial 10 seconds after Ca^{2+} was added.

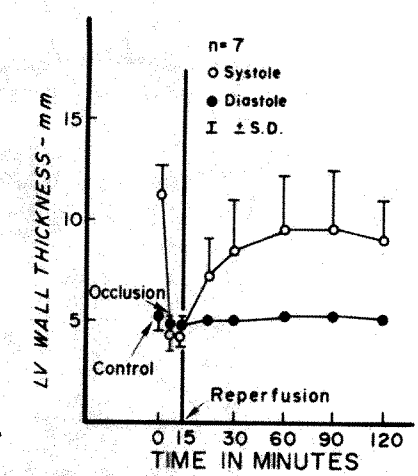

FIGURE 4. Systolic and diastolic left ventricular (LV) wall thickness (mm, mean ± standard deviation [SD]) for all 7 animals with coronary occlusion of 15 minutes. Results obtained during the control period, occlusion, and reperfusion are illustrated.

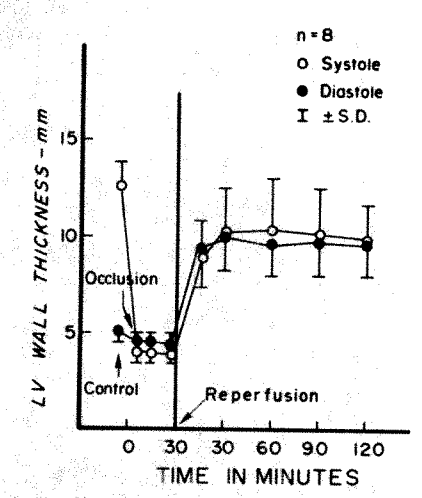

FIGURE 5. Systolic and diastolic left ventricular wall thickness (mm, mean ± SD) for all 8 animals with coronary occlusion of 30 minutes. Results obtained during the control period, occlusion, and reperfusion are illustrated.

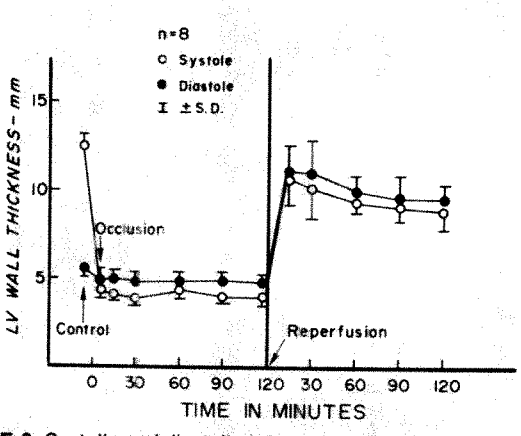

FIGURE 6. Systolic and diastolic left ventricular wall thickness (mm, mean ± SD) for all 8 animals with a coronary occlusion of 120 minutes is shown. Results obtained during the control period, occlusion, and reperfusion are illustrated.

TABLE I Mitochondrial Oxidative Phosphorylation After 15, 30, or 120 Minutes of Coronary Occlusion and 120 Minutes of Reperfusion

Group	QO_2 (ng atoms O/mg/min)	ATP/O	RCI
15 minute ischemia			
Control LV	287 ± 38	2.7 ± 0.3	9 ± 2
Reperfused LV	268 ± 36	2.4 ± 0.3	8 ± 2
30 minute ischemia			
Control LV	287 ± 50	2.6 ± 0.2	10 ± 3
Reperfused LV	133 ± 59*	1.7 ± 0.3*	4 ± 1*
p	<0.001	<0.001	<0.001
120 minute ischemia			
Control LV	288 ± 65	2.6 ± 0.2	9 ± 2
Reperfused LV	11 ± 4*	0.4 ± 0.1*	1.5 ± 0.5*
p	<0.001	<0.001	<0.001

* In addition to the p values shown between the control and reperfused left ventricle (LV) in each group, there was a significant difference ($p < 0.001$) in the reperfused LV of the 30 and 120 minute ischemia groups compared with the 15 minute reperfused LV.

ATP = adenosine triphosphate; QO_2 = oxygen consumption; O = oxygen; RCI = respiratory control index.

TABLE II Mitochondrial Ca^{2+} Content and Myocardial Ca^{2+} and ATP Content After 15, 30, or 120 Minutes of Ischemia and 120 Minutes of Reperfusion

Group	Mitochondrial Ca^{2+} (nmol/mg)	Tissue Ca^{2+} (μmol Weight)/g Wet	ATP (nmol/mg Protein)
15 minute ischemia			
Control LV	14 ± 4	1.2 ± 0.2	6.8 ± 3.6
Reperfused LV	16 ± 5	1.3 ± 0.2	4.8 ± 1.4
30 minute ischemia			
Control LV	13 ± 3	1.2 ± 0.3	6.6 ± 3.9
Reperfused LV	50 ± 11*	5.9 ± 1.9*	3.2 ± 1.8†
p	<0.001	<0.001	<0.01
120 minute ischemia			
Control LV	17 ± 5	1.2 ± 0.2	6.7 ± 3.0
Reperfused LV	43 ± 24*	5.0 ± 0.9*	1.2 ± 1.0*
p	<0.001	<0.001	<0.001

* In addition to p values shown between control and reperfused left ventricle (LV) in each group, there was a significant difference ($p < 0.001$) in the reperfused LV of 30 and 120 minute ischemia groups when compared with the 15 minute reperfused LV.

† Difference ($p < 0.01$) between reperfused LV in 30 minute group compared with 15 minute reperfused LV.

A slight decrease in Ca^{2+}-induced respiration and H^+ ejection was observed in the 15 minute ischemia group. This Ca^{2+}-induced respiration and H^+ ejection decreased from 126 ng atoms O/mg/min and 284 nmol H^+/mg/min in the control group to 62 and 144, respectively, in the 30 minute ischemia group. These respective values were further decreased to 8 ng atoms O/mg/min and 17 nmol H^+/mg/min in the 120 minute ischemia group. Furthermore, Ca^{2+} accumulation by mitochondria 1 minute after the addition of $^{45}Ca^{2+}$ was 167, 142, 79, and 10 nmol/mg of protein for the control group and 15, 30, and 120 minute ischemia groups, respectively.

Mitochondrial Ca^{2+} content and myocardial tissue levels of Ca^{2+} and ATP are shown in Table II. There was no difference between control myocardium and 15 minute ischemic myocardium for mitochondrial Ca^{2+} and tissue Ca^{2+} content. However, mitochondrial and myocardial Ca^{2+} levels increased significantly in the 30 and 120 minute ischemia groups. ATP content of tissue after 15 minutes of ischemia and 2 hours of reperfusion was only slightly decreased whereas a progressive decrease was observed in the 30 and 120 minute ischemia groups.

Table III shows that Ca^{2+} uptake by isolated sarcoplasmic reticulum vesicles decreased slightly in the

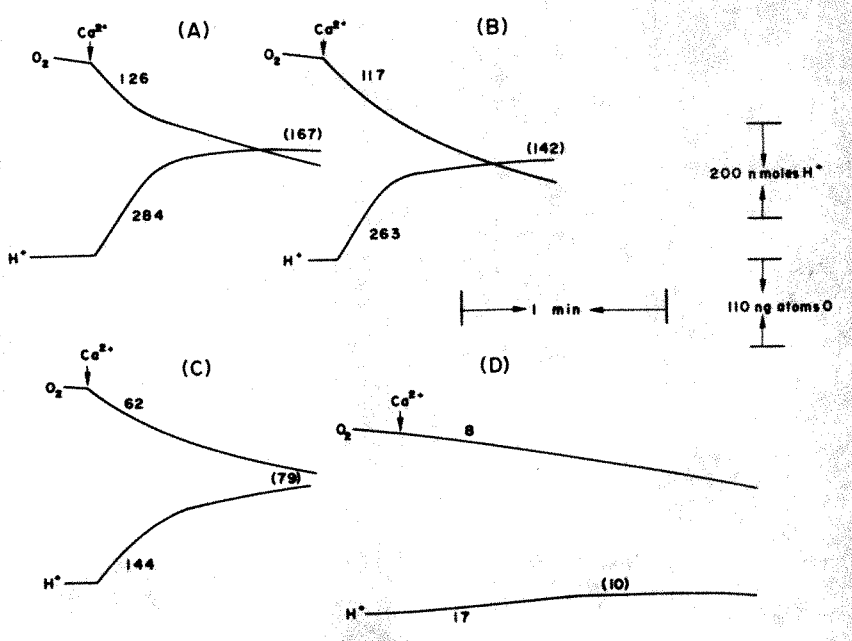

FIGURE 7. Oxygen and pH electrode tracings showing the rate of Ca^{2+}-induced respiration and H^+ ejection of mitochondria. The experimental system contains 1.0 m*M* Hepes buffer, pH 7.4, 100 m*M* KCl, 100 m*M* sucrose, 1 m*M* potassium phosphate monobasic, and mitochondria (2.0 to 2.2 mg protein). Ca^{2+} (400 nmol) was added to the incubation mixture to initiate the reaction in a final volume of 2.0 ml at 30°C as indicated. The number adjacent to each oxygen and pH electrode tracing represents the rate of oxygen consumption (ng atoms O/mg/min) and H^+ ejection (nmol H^+/mg/min) by mitochondria. Numbers included in parentheses represent $^{45}Ca^{2+}$ uptake by mitochondria (nmol Ca^{2+}/mg protein) 1 minute after $^{45}Ca^{2+}$ was added. **A,** mitochondria from control left ventricle; **B,** mitochondria from 15 minute ischemic and reperfused left ventricle; **C,** mitochondria from 30 minute ischemic and reperfused left ventricle; **D,** mitochondria from 120 minute ischemic and reperfused left ventricle.

TABLE III Calcium Uptake by Sarcoplasmic Reticulum Vesicles

Group	Rate of Ca^{2+} Uptake (nmol/mg/min)	
	Control LV	Reperfused LV
15 minute ischemia	249 ± 41	201 ± 24
30 minute ischemia	239 ± 26	113 ± 47*
120 minute ischemia	255 ± 28	27 ± 14*

* Significant difference from reperfused left ventricle (LV) in the 30 and 120 minute ischemia groups when compared with the 15 minute ischemia group, $p < 0.001$. Incubation system contained 20 m*M* Tris maleate buffer, pH 6.9, 100 m*M* KCl, 10 m*M* $MgSO_4$, 3 m*M* sodium oxalate, 0.3 m*M* murexide, Ca^{2+} (400 nmol), sarcoplasmic reticulum vesicles (0.4 mg), 4 μg oligomycin (to inhibit a possible contamination from any mitochondrial Ca^{2+} accumulation), and 3 m*M* ATP in a final volume of 3 ml at 23°C. The rate of Ca^{2+} uptake is determined from the dual-beam spectrophotometric trace as previously described.[25]

15 minute ischemia group when compared with those from the control left ventricle. The rate of Ca^{2+} uptake by sarcoplasmic reticulum vesicles was further decreased from 239 and 255 nmol/mg/min in control tissue to 113 and 27 in the 30 and 120 minute ischemia groups, respectively.

Water content of the control myocardium was 79.1 ± 0.7%. In the 30 minute ischemia group it was 83.3 ± 0.8 ($p < 0.01$) and in the 120 minute group it was 82.9 ± 0.8 ($p < 0.01$). Data for water content were unavailable for the 15 minute group.

Discussion

Reduced myocardial performance after transient coronary occlusion followed by reperfusion: Echocardiographic measurements of wall thickness show lack of systolic thickening and marked thinning during both systole and diastole promptly after acute coronary occlusion. This thinning persisted throughout the length of occlusion in all 3 groups of animals. Abrupt loss of contractile activity and wall thinning with ischemia has been reported by others.[10,29,30] The mechanism of these changes has been attributed to sudden loss of oxygen and loss of substrate delivery to the energy-producing sites, with cessation of ATP formation. Without energy production there is an inability to generate or maintain tension, an increase in compliance,[31] and passive thinning of the involved segment resulting from pressure developed in the left ventricle by the remaining normal myocardium. This effect is recognized grossly by systolic expansion of the ischemic zone. In our study reperfusion of the ischemic zone after 30 and 120 minutes of ischemia resulted in thickening of the left ventricular wall; however, this was not true for the 15 minute group. In the 30 minute ischemia group, there was not a significant return of ventricular performance as a whole, although 3 of 8 animals in this group did show evidence of slight systolic thickening.

Recently, myocardial perfusion was shown to be abnormal for prolonged periods after transient ischemia in the dog, and contractility abnormalities were previously documented to persist beyond the return of metabolic function toward normal.[32] Our data substantiate the latter observations, but the mechanisms of reduced myocardial perfusion and performance persisting after transient coronary occlusion followed by reperfusion remain unknown.

Mechanism of diastolic wall thickening with reperfusion: The mechanism of wall thickening in diastole with reperfusion has been studied by others. Gaasch and Bernard[10] described transient increases in left ventricular wall thickness on reperfusion after relatively short periods of ischemia. These changes were judged to be related to the acute increase in coronary flow (reactive hyperemia) that occurs on ligature release. As reactive hyperemia is a transient phenomenon, it would seem unlikely that the prolonged increase in left ventricular wall thickness observed in our present experiments resulted merely from an increase in blood volume of involved myocardium. Although some investigators[12,33] showed a significant increase in edema formation and myocardial cell swelling with reperfusion, the small increase in tissue water seen in our study would not seem to account for the marked increase in wall thickness. Although focal microscopic edema may have been present, it is unlikely that gross edema plays a significant role in reperfusion-induced wall thickening.

Intramyocardial hemorrhage with reperfusion after ischemia times of 1 hour or longer was described[34] and in our study was prevalent on microscopic sections from animals after 120 minutes of ischemia. However, absence of or slight hemorrhage in the 30 minute ischemia group and total absence in the 15 minute ischemia group indicate that this mechanism is not the one responsible for the thickened left ventricular wall. Recent studies[35,36] suggest that the extent of hemorrhage associated with reperfusion is the consequence of injury due to ischemia rather than to reperfusion.

The role of mitochondrial damage in reperfusion-induced wall thickening is important, as evidenced by marked decreases in mitochondrial function in the 30 and 120 minute ischemia groups. Mitochondria isolated from reperfused areas of 30 minutes or more of ischemia were unable to efficiently generate ATP. The abnormalities of mitochondrial configurations and structures in irreversibly ischemic or ischemic-reperfused myocardium were previously reported.[20,37,38] Some electron-dense granules were observed in the swollen mitochondria in the ischemic myocardium on reperfusion. These granules were suggested to be either lipid components of the cell or some type of calcium phosphate complexes.[39,40] It is difficult to correlate closely the extent of morphologic integrity with biochemical alterations in these mitochondrial preparations. Electron-dense granules and swollen mitochondria have been observed in both sliced tissue sections and isolated preparations from irreversible ischemic myocardium.[20,37,38,40] It is generally believed that a certain degree of damage has already taken place in vivo during the ischemic insult before isolation procedures begin. Some investigators suspect that mechanical disruption

associated with isolation may also induce some degree of damage to mitochondrial structure and function, particularly to those from ischemic-reperfused myocardium. However, it is difficult to assess how much functional impairment is due to ischemic insult versus mechanical disruption. Nevertheless, this study shows a positive correlation between the abnormality of ventricular wall thickening and the alteration of mitochondrial function. Adverse effects on mitochondrial function were also previously demonstrated by Wood et al.[32] in the dog model. After short occlusion times of 5 and 10 minutes with reperfusion, mitochondrial function returned toward normal. However, with longer ischemic periods, mitochondrial function was depressed. Thus, the alteration in the biochemical function of mitochondria which results in impaired energy production may be one factor among others, such as capillary damage and cell swelling,[41–44] contributing to the development and persistence of regional wall thickening.

Calcium content of reperfused ischemia myocardium: A striking abnormality is the 5-fold increase in calcium content of tissue of the reperfused left ventricle from both 30 and 120 minute ischemia groups and the increased mitochondrial calcium. This increase was previously described.[43,44] Furthermore, calcium ion (Ca^{2+}) accumulation by mitochondria and sarcoplasmic reticulum vesicles was markedly deranged in both groups. These high levels of calcium ion in ischemic myocardium may have resulted from the inability to pump calcium ion out of the cell because of a defect in Ca^{2+}-dependent ATPase of the sarcolemma membrane as well as from the limited capacities of sarcoplasmic reticulum vesicles and mitochondria to remove cellular calcium ion. This, in turn, inhibits ATP production by mitochondria.[45] These high levels of calcium ion in tissue and low ATP produced by mitochondria may result in delay or failure of myocardial relaxation, a thickened left ventricular wall, and ischemic contracture with little or no return of function. The sequence of events described in our experiments is similar to that described by Cooley et al.[46] in the "stone heart syndrome" which occasionally developed in patients placed on cardiopulmonary bypass with normothermic ischemic arrest and may account for the "paradox of necrosis" in areas of revascularization after bypass surgery as described by Bulkley and Hutchins.[7] A recent study[47] describes failure of myocardial relaxation or ischemic contracture in rabbit hearts made ischemic and then reperfused. Accumulation of calcium in mitochondrial fractions isolated from the reperfused left ventricle paralleled the severity of contracture and lack of diastolic relaxation. In animals in that study treated with a calcium antagonist, nifedipine, contractures did not develop with reperfusion. Recently a study[48] using verapamil showed a favorable effect with better preservation of ATP generation and a more normal content of tissue and mitochondrial calcium ion.

Application to human experimental data: The findings of this study may relate to left ventricular performance and biochemical alterations of myocardium in man after reperfusion with thrombolytic agents in thrombotic acute myocardial infarction, after prolonged severe coronary spasm resulting in severe ischemia or infarction,[49,50] or in regionally ischemic areas of the myocardium after bypass surgery in some patients.[7] The extent of damage to the myocardium in these instances may ultimately be related to occlusion or reperfusion times and the presence or absence of coronary collaterals. The problem of nonuniformity of cellular damage and the potential for salvage of jeopardized cells has recently been critically discussed, particularly as it relates to the border zone of an infarction.[51] The complex issues of pathogenesis of myocardial infarction—thrombosis, spasm, and altered platelet activity as well as the dynamics of atherosclerosis—call for caution in extrapolation of experimental data to man; the need for careful studies in these areas was emphasized by Muller et al.[52] The arbitrary time period of 2 hours of reperfusion in our experimental protocol is a limiting factor in clinical application. Nevertheless, it is apparent that time after the onset of severe ischemia is critical if reperfusion is to reverse severe tissue damage and death.

The choice of the animal model deserves comment. There is no ideal model to simulate the usual circumstances of noteworthy coronary atherosclerosis that exist before acute ischemia.[53] The dog is frequently used because of the presence of preexisting coronary collateral vessels thought to resemble the situation in man. However, in acute infarction in man, collateral vessels, as determined by angiography, may be absent.[54] The pig is essentially free of coronary collateral vessels[17] and may serve as an acceptable model of this nature. Because of the interaction of coronary collateral circulation of the animal model chosen and varying ischemia and reperfusion time protocol, our data expand the information available in this vital area and serve as a comparison with animal models with different coronary perfusion patterns.

In conclusion, this study shows that ischemia for 30 or 120 minutes results in damaged myocardial cell membranes, allowing accumulation of calcium ion in tissue and mitochondria on reperfusion of the ischemic zone. This calcium ion accumulation then interferes with mitochondrial ATP production and apparently inhibits myocardial relaxation probably related in part to high calcium ion and low ATP levels. Marked diastolic thickening and lack of systolic thickening in the reperfused zone are observed. Relatively normal systolic thickening and diastolic thinning, mitochondrial function, sarcoplasmic reticulum calcium ion uptake, myocardial calcium ion, and ATP content after 15 minutes of ischemia followed by reperfusion were observed. These findings suggest that an irreversible cell membrane defect occurs between 15 and 30 minutes of ischemia if followed by reperfusion, and that this defect allows calcium accumulation resulting in a reduction of myocardial performance including effective diastolic relaxation and systolic contraction.

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Effect of Intraaortic Balloon Counterpulsation on Regional Myocardial Blood Flow and Oxygen Consumption In the Presence of Coronary Artery Stenosis: Observations in an Awake Animal Model

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The mechanism by which intraaortic balloon pumping ameliorates myocardial ischemia in patients with unstable angina pectoris is uncertain. Accordingly, the following study was performed to determine the effect of intraaortic balloon pumping on regional myocardial blood flow and myocardial oxygen consumption (MVO_2) distal to severe coronary artery stenosis. Nine closed chest conscious pigs were instrumented with a 7.5 mm long plastic stenosis which reduced vessel diameter by 82%. Measurements of hemodynamics, regional myocardial blood flow (microsphere technique) and MVO_2 were made (1) before intraaortic balloon pumping, (2) at the end of 15 to 20 minutes of intraaortic balloon pumping, and (3) 20 minutes after its discontinuation.

Control endocardial blood flow ($ml \cdot min^{-1} \cdot g^{-1}$) distal to the stenosis (1.04 ± 0.20, mean ± 1 standard deviation [SD]) was less than endocardial flow in myocardium perfused by the unobstructed circumflex coronary artery (1.67 ± 0.77, $p < 0.01$). Likewise, control distal zone epicardial flow (1.16 ± 0.36) was reduced in comparison with control circumflex zone epicardial flow (1.48 ± 0.60, $p < 0.01$).

In response to intraaortic balloon pumping rate-pressure product declined versus control (10,300 ± 2,090 [SD] mm $Hg \cdot min^{-1}$ to 9,110 ± 2,010, $p < 0.005$), whereas aortic mean diastolic pressure (mm Hg) increased versus control (109.0 ± 9.9 to 121.0 ± 13.8, $p < 0.01$). Distal coronary mean diastolic pressure did not change in response to intraaortic balloon pumping (61.9 ± 13.0 to 68.7 ± 16.5, p = NS). Likewise, endocardial blood flow ($ml \cdot min^{-1} \cdot g^{-1}$) distal to the stenosis did not change during intraaortic balloon pumping (1.00 ± 0.24) versus control (1.04 ± 0.20). In contrast, during intraaortic balloon pumping epicardial blood flow distal to the stenosis declined versus control (1.16 ± 0.36 to 1.01 ± 0.27, $p < 0.05$). Regional MVO_2 ($ml \cdot min^{-1} \cdot 100\ g^{-1}$) distal to the stenosis also decreased versus control in response to intraaortic balloon pumping (12.90 ± 3.55 to 10.30 ± 2.52, $p < 0.05$). Furthermore, regional MVO_2 correlated well ($r = 0.74$, $p < 0.002$) with rate-pressure product.

Thus, intraaortic balloon pumping reduces myocardial oxygen demand but does not improve blood flow distal to a severe coronary stenosis; (2) blood flow distal to a severe stenosis may fail to increase with intraaortic balloon pumping because (A) distal coronary mean diastolic pressure may not increase, and (B) blood vessels distal to the stenosis tend to autoregulate in response to a decline in myocardial oxygen demand; and (3) intraaortic balloon pumping ameliorates myocardial ischemia in patients with unstable angina pectoris primarily by reducing oxygen demand rather than by increasing oxygen supply.

The use of intraaortic balloon pumping to produce arterial counterpulsation has been shown effective in relieving pain and controlling myocardial ischemia in patients with unstable angina pectoris.[1–4] Many patients generally have 1 or more severely stenosed but patent coronary arteries. The mechanism(s) by which arterial counterpulsation ameliorates myocardial ischemia in these patients has not been clearly defined. Because arterial counterpulsation reduces ventricular afterload and increases diastolic pressure in the aorta,[5–9] it may be effective either by reducing myocardial oxygen demand or by increasing oxygen supply, or both. However, firm proof that arterial counterpulsation actually increases blood flow distal to a severe coronary artery stenosis is not available. Gill et al.[10] measured an increase in myocardial blood flow distal to severe stenosis

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of a circumflex coronary artery in an open chest canine preparation. However, in their study heart rate was not controlled or commented on. Thus, an increase in heart rate could have occurred during counterpulsation and may have been responsible for the increase in the observed flow. Furthermore, although many investigators have examined the effects of intraaortic balloon pumping on regional blood flow distal to a ligated coronary artery, the results have been inconsistent; some investigators[11–13] reported an increase in collateral flow in response to balloon pumping alone whereas others[14–17] observed no change in flow. In light of these considerations we performed studies in a closed chest porcine model instrumented with a severe intraluminal coronary artery stenosis[18] in order to test the hypothesis that arterial counterpulsation is effective in relieving myocardial ischemia in the setting of a stenosed but patent coronary artery primarily by virtue of its ability to reduce myocardial oxygen demand rather than by increasing oxygen supply.

Methods

Animal preparation: Nine farm-bred pigs (mean weight 41.9 kg, range 35.6 to 49.6) were anesthetized with halothane (0.5 to 1.5%) and nitrous oxide, intubated, and ventilated with a volume-cycled respirator. After the animal was heparinized (225 IU·kg^{-1}) a 6Fr end hole catheter was inserted into the left brachial artery and advanced into the subclavian artery. This line was used to monitor pressure, to obtain samples of blood for pH, PO_2 and PCO_2, and for withdrawal of blood for determination of regional myocardial blood flow (microsphere technique). A 40 ml intraaortic balloon (PERCOR-40™, Datascope, Paramus, New Jersey) was inserted in the left femoral artery. The distal end of the balloon was advanced under fluoroscopic control to the arch of the aorta and positioned just below the subclavian artery. The right femoral artery was used to insert an 8Fr angiographic catheter which was passed retrograde under fluoroscopic guidance into the left atrium through the left ventricle. This catheter was used to administer radioactive microspheres. A 7Fr "head-hunter" catheter (USCI, Billerica, Massachusetts) inserted into the right internal jugular vein was advanced under fluoroscopic control into the coronary sinus and then to the proximal portion of the anterior interventricular vein. This catheter was used to sample coronary venous blood draining myocardium in the distribution of the left anterior descending coronary artery.

The animal's heart was paced at a constant rate throughout the study by means of a 7Fr bipolar catheter positioned in the proximal portion of the coronary sinus. An 8Fr Amplatz catheter was inserted into the right carotid artery and advanced under fluoroscopic control to the left anterior descending coronary artery. The artery was visualized by hand injection of 3 to 5 ml Renografin-76™ after which an 0.018 Teflon®-coated guidewire with a 3 cm floppy distal end was inserted into the vessel. The Amplatz catheter was removed and a plastic stenosis (7.5 mm long, outside diameter 3.5 mm, inside diameter 0.625 mm) loaded onto the wire and advanced down it into the proximal 3rd of the coronary artery. The wire was quickly removed, leaving the stenosis in place. The stenosis contained a 2nd lumen into which the distal end of a 1.0 mm diameter, 70 cm long plastic catheter had been attached before placement of the stenosis. The distal end of the catheter was open to the distal end of the stenosis and was used to record distal coronary pressure in the left anterior descending artery. Finally, an 8Fr micromanometer tip catheter (Millar Instruments, Houston, Texas) was inserted into the left ventricle through the right carotid artery. This completed the preparation of the animal. After instrumentation had been accomplished, all cutdown sites were closed and the animal permitted to awaken from anesthesia. Small doses (20 to 40 mg) of sodium thiamylol were then given intravenously throughout the study to insure that the animal was comfortable and rested quietly. Although sedated, the animal breathed spontaneously, was awake, and had brisk corneal reflexes.

Experimental protocol: On the day before the study each animal was given aspirin (150 mg orally) to prevent platelet aggregation within the lumen of the stenosis.[19] After instrumentation had been completed, propranolol (1 to 2 mg·kg^{-1}) was given intravenously. After 15 to 20 minutes after a stable baseline heart rate had been established, atrial pacing was begun at a rate of 10 to 15 beats/min above baseline. Pacing was continued at this rate for the remainder of the study. Control measurement of hemodynamics (see later), regional myocardial blood flow, and regional oxygen metabolism (see later) were then obtained after 15 minutes of atrial pacing at a constant rate. Next, the intraaortic balloon pump was turned on and counterpulsation maintained for 15 to 20 minutes. The balloon pump was phased with a Datascope control unit (model 3510) so as to produce maximal attainable systolic unloading of the left ventricle along with maximal attainable augmentation of diastolic pressure in the aorta. At the end of 15 to 20 minutes of balloon counterpulsation, hemodynamic, regional myocardial blood flow, and metabolic measurements were repeated. The balloon pump was then turned off and 20 minutes allowed to elapse after which all measurements were repeated. Thereafter, the animal was killed and the heart removed and sectioned for determination of microsphere activity (see later).

Acquisition and analysis of hemodynamic data: All pressures except those from the left ventricle were obtained with fluid-filled catheters and Hewlett-Packard transducers (model 1280). Left ventricular pressures were recorded from a solid state micromanometer tip catheter which was balanced electronically and calibrated with reference to pressure obtained from the fluid-filled catheter in the left atrium. The frequency response of the narrow lumen catheter used to record pressure distal to the stenosis exhibited an acceptable frequency response (3 db roll-off at 5.5 Hz) when tested in vitro. Because the heart rates encountered in this study were less than 1.5 Hz in all but 1 animal in which the rate was 1.83 Hz, it can be shown that 90 to 95% of all phasic information in the arterial wave form could be recovered with this system.[20]

All pressure signals were digitized simultaneously on-line with the aid of a PDP 11/40 computer system and 12 bit analog-to-digital converter. Because pressures were sampled at 200 Hz over a dynamic range of 0 to 300 mm Hg, we were able to resolve pressure changes to ±0.07 mm Hg. Ten second data acquisitions were obtained for each experimental condition. The animal's electrocardiogram (lead II) also was digitized on-line along with the pressure signals in order to detect the R wave that was used for timing purposes. The signals were then formatted with respect to the R wave into an average cardiac cycle using the forward and reverse averaging technique of Bacharach et al.[21] The computer also was used to determine maximal, minimal, mean systolic, mean diastolic, and overall mean pressure in the left ventricle, aorta, and distal coronary artery for each phase of the study. Left ventricular end-diastolic pressure, the left ventricular tension-time index (area under the systolic portion of the left ventricular pressure trace multiplied by heart rate [per second]), and maximal positive left ventricular dP/dt (first derivative of left ventricular pressure) also were determined by the

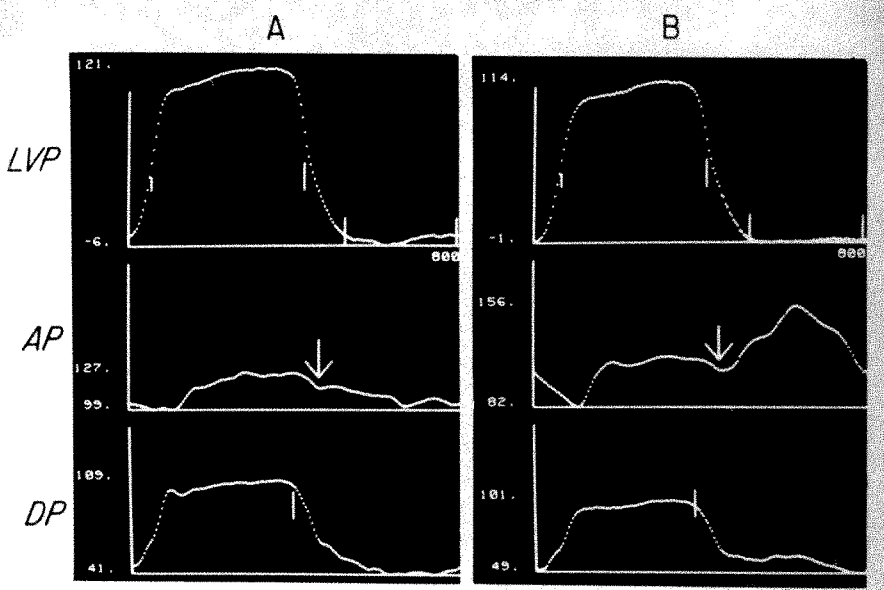

FIGURE 1. Left ventricular (LVP), aortic (AP), and distal coronary artery (DP) pressure wave forms for an average cardiac cycle obtained under control conditions (**panel A**) and during arterial counterpulsation (**panel B**). The **vertical bars** on the left ventricular pressure trace indicate computer-identified points for maximal positive and negative left ventricular dP/dt. Similarly, the **arrow** on the aortic pressure trace indicates the computer-identified position of the dicrotic notch. Mean diastolic pressure (area under the curve divided by time) was determined between the dicrotic notch and the point of minimal aortic pressure. The **vertical bar** on the distal coronary pressure trace marks the computer identified onset of diastole. This point was defined as the point that preceded the point of maximal negative left ventricular dP/dt by 20 ms. End-diastole was defined as the point on the distal pressure trace that coincided with the R wave of the electrocardiogram. Note that counterpulsation produced a substantial increase in aortic diastolic pressure along with a decrease in left ventricular mean systolic pressure. Distal coronary mean diastolic pressure also was augmented by counterpulsation in this animal, although the pressure wave form was not altered substantially.

computer. Two examples of typical records obtained from 1 of the animals used in the study are shown in Figure 1. All hemodynamic measurements for each phase of the study were made from the computer-generated average cardiac cycle.

Acquisition of regional myocardial oxygen consumption data: Paired samples (2 to 3 ml) of arterial and anterior interventricular vein blood were obtained for determination of oxygen content (Lex-O_2-CON Instrument, Lexington Instruments, Waltham, Massachusetts) during each phase of the study. Samples were obtained immediately after each determination of regional myocardial blood flow. Blood samples were collected in heparinized glass syringes and immediately placed on ice for subsequent analysis at the end of the study. Oxygen content (vol/100 ml) was determined in duplicate for each sample and values were accepted only if both readings agreed to within ± 0.2 vol/100 ml. Regional myocardial oxygen consumption ($ml \cdot min^{-1} \cdot 100\ g^{-1}$) was calculated as the product of transmural regional myocardial blood flow distal to the stenosis and the arterial-anterior interventricular vein oxygen difference.

After the animal had been killed the position of the distal end of the anterior interventricular vein catheter was carefully noted with respect to (1) its location in relation to the proximal end of the artificial stenosis, and (2) the presence of any large venous tributaries arising from myocardium not perfused by the stenosed portion of the left anterior descending artery. We observed no major venous tributaries arising from normally perfused myocardium emptying into the anterior interventricular vein distal to the distal end of the indwelling catheter in any of the animals in which regional myocardial oxygen consumption data are reported (n = 7). The distal end of the anterior interventricular vein catheter came to rest an average of 2.2 cm (range 0.8 to 3.5) proximal to the level of the proximal end of the artificial stenosis.

Determination of regional myocardial blood flow: Regional myocardial blood flow was determined by the microsphere technique.[22] For each experimental condition approximately 4×10^6 radiolabeled microspheres (15 μm diameter, 85 to 105 μCi total radioactivity) were injected through the left atrial catheter. A precisely timed, 2 minute reference collection of arterial blood was begun 15 to 30 seconds before injection of the radiolabeled microspheres. Blood was withdrawn at a constant rate (10 ml/min) from the subclavian artery catheter into a 50 ml preweighed glass syringe by means of a Harvard pump. It also should be noted that (1) a different radioisotope was chosen at random for each flow determination, and (2) the microspheres were suspended in 10% dextran with 0.01% Tween-80™ and sonically dispersed for 15 minutes before each injection. Finally, to precisely label myocardium distal to the stenosis, approximately 300,000 radiolabeled microspheres (15 μm diameter, total activity approximately 4.0 μCi) were injected into the distal coronary pressure catheter at the end of the study. The animal was killed by giving a large intravenous dose of sodium thiamylol (200 to 300 mg) and 3 to 5 minutes later a lethal dose of potassium chloride through the left atrial catheter.

After the animal was killed the heart was removed and sectioned for determination of microsphere activity. The free wall of the left ventricle was removed from the heart after which epicardial blood vessels and fat were carefully trimmed away. Next, the ventricle was cut into cubes weighing 2 to 3 g and the location of each carefully noted on a diagram of the free wall of the ventricle. Each cube was divided into endocardial and epicardial halves and placed in a preweighed plastic vial. The vials were reweighed and then counted in a gamma well counter (Packard Instruments, Downer Grove, Illinois). A computer was used to correct for spillover of counts from 1 isotope into the window of another and to calculate regional myocardial blood flow ($ml \cdot min^{-1} \cdot g^{-1}$) in each tissue sample. For purposes of analysis the free wall was divided into 2 zones: 1 at the base of the heart perfused by the circumflex coronary artery (circumflex zone) and the other perfused by the left anterior descending artery distal to the stenosis (distal zone). The latter area was readily identified because it contained a high concentration of marker microspheres ($7{,}000 \cdot g^{-1}$ or greater), whereas the circumflex zone contained none.

Additional animals (n = 5): A total of 5 additional animals were studied to confirm that the artificial stenosis caused regional myocardial ischemia under basal conditions (n = 2) and to facilitate interpretation of changes in regional myo-

TABLE I Hemodynamic Results (Mean ± 1 SD) of Intraaprtic Balloon Pumping (IABP) in 9 Pigs With a Severe Coronary Artery Stenosis

	Control I	IABP	Control II
Heart rate (min^{-1})	85.4 ± 13.7	85.2 ± 13.9	86.6 ± 13.6
LV systolic pressure (mm Hg)	120.0 ± 7.5	106.0 ± 8.4*	118.0 ± 10.5
LV end-diastolic pressure (mm Hg)	7.2 ± 4.6	8.0 ± 4.6	5.7 ± 4.8
LV maximal positive dP/dt (mm $Hg \cdot s^{-1}$)	1,530 ± 297	1,380 ± 370†	1,440 ± 297
Rate pressure product mm $Hg \cdot min^{-1}$)	10,300 ± 2,090	9,110 ± 2,010*	10,300 ± 2,520
Tension-time index (mm $Hg \cdot s^{-1}$)	50.1 ± 7.3	42.8 ± 7.9*	47.1 ± 9.6†
Aortic mean pressure (mm Hg)	117.0 ± 10.5	114.0 ± 14.2	115.0 ± 12.0
Aortic mean diastolic pressure (mm Hg)	110.0 ± 13.7	121.0 ± 13.8‡	110.0 ± 11.4
Distal coronary mean (mm Hg)	80.8 ± 9.0	76.1 ± 11.3	75.2 ± 13.5
Distal coronary mean diastolic pressure (mm Hg)	61.9 ± 13.0	68.7 ± 16.5	59.7 ± 18.9

* $p < 0.005$ versus control I. † $p < 0.05$ versus control I. ‡ $p < 0.01$ versus control I.
LV = left ventricular.

cardial blood flow and oxygen consumption that occurred in response to balloon pumping (n = 3). Ultrasonic length sensors (Norland Corp., Fort Atkinson, Wisconsin) were inserted under sterile conditions near the endocardial surface of the left ventricle in each pig. One pair of sensors was placed near the base of the heart in an area perfused by the circumflex coronary artery, whereas the other pair was placed in the anterior free wall of the left ventricle in a region perfused by the distal ramifications of the left anterior descending coronary artery. A small polyethylene catheter (outside diameter 1.2 mm) was inserted into the left atrium and secured with a purse-string suture at the time of surgery. Both the catheter and wires from the piezoelectric crystals were tunneled through the chest wall and secured under the animal's skin behind the neck. Thereafter, the animal's chest was closed and air evacuated. Seven to 10 days later when recovered from surgery, the animal was returned to the laboratory for study.

In 2 animals anesthetized with halothane and nitrous oxide a 7Fr bipolar pacing catheter was placed in the coronary sinus and pacing was begun at a rate 10 to 15 min^{-1} above the animal's sinus rate. Once a steady state had been achieved for 10 to 15 minutes, radioactive microspheres were injected into the left atrial catheter to measure regional myocardial blood flow. Hemodynamics (heart rate, arterial pressure) and regional systolic function (ultrasonic length sensors) were recorded at the same time. Thereafter, the artificial stenosis was inserted into the animal's left anterior descending coronary artery and repeat measurements of all experimental variables obtained were 10 and 30 minutes later. As described previously, myocardium distal to the stenosis was objectively demarcated by infusion of a separate marker set of microspheres directly into the pressure catheter attached to the stenosis. The animal was then killed and the heart removed to determine microsphere activity and to confirm the location of the length sensors.

The other 3 animals were used to document the effect of balloon counterpulsation on regional myocardial function. These animals were prepared and instrumented in exactly the same fashion as described in Section 1 on animal preparation. After instrumentation was completed the animals were permitted to awaken from anesthesia. All animals were studied after beta blockade with propranolol and with heart rate controlled by means of atrial pacing at 10 to 15 min^{-1} above the animal's intrinsic rate. Once a steady state had been achieved, control measurements of regional myocardial blood flow, oxygen metabolism, systolic function, and hemodynamics were obtained. Next, the intraaortic balloon pump was turned on and phased so as to produce maximal systolic unloading along with maximal attainable augmentation of aortic diastolic pressure. At the end of 15 to 20 minutes of counterpulsation repeat measurements of all experimental variables were made. Thereafter, marker microspheres were given through the perfusion catheter and the animal was killed. The heart was removed and sectioned for determination of microsphere activity and to confirm the location of the length sensors.

Statistical methods: The significance of group mean changes (versus control) for hemodynamic, regional myocardial blood flow, and oxygen metabolism variables in response to arterial counterpulsation were assessed by means of a blocked 1-way analysis of variance and Dunnett's test.[23] Results were considered statistically significant when $p < 0.05$. All values are expressed as mean ±1 SD. Correlations between variables were assessed by means of a simple linear regression analysis.

Results

Group I (9 Animals Studied Before, During, and After Intraaortic Balloon Pumping)

Hemodynamics (Table I): As required by the study design, heart rate did not change significantly versus control in response to intraaortic balloon pumping. In contrast, peak left ventricular systolic pressure, rate pressure product (heart rate × peak left ventricular pressure), and tension time index all declined significantly ($p < 0.005$) versus control during arterial counterpulsation. As expected, intraaortic balloon pumping also produced a significant ($p < 0.01$) increase (versus control) in aortic mean diastolic pressure. Despite the fact that aortic mean diastolic pressure increased with arterial counterpulsation there was no significant change in distal coronary mean diastolic pressure for the group as a whole although 5 of 9 animals did exhibit an increase (18.1 ± 3.3% above control levels). However, distal coronary mean diastolic pressure failed to increase in 4 of the animals primarily because augmentation of early diastolic pressure by balloon inflation was offset by considerable lowering of late diastolic pressure when the balloon was deflated. Accordingly, the *mean* value of diastolic pressure distal to the stenosis failed to change versus control in these animals. Both distal coronary mean pressure and aortic mean pressure showed no significant change in response to balloon pumping. Left ventricular end-diastolic pressure did not change significantly during the study. Maximal positive

left ventricular dP/dt declined significantly in response to arterial counterpulsation. After discontinuation of balloon pumping all hemodynamic variables returned to control levels with the exception of the tension time index which remained modestly but significantly depressed versus its initial control value.

Regional myocardial blood flow (Table II; Fig. 2): Under control conditions, regional myocardial blood flow was reduced significantly in both endocardium and epicardium of the distal zone in comparison with respective flows in the circumflex zone. The ratio between distal and circumflex zone flows (endocardium and epicardium) did not change significantly during the study. In response to intraaortic balloon pumping both endocardial and epicardial blood flow in both distal and circumflex zones tended to decline compared with control. However, only the decrease in distal zone epicardial flow attained statistical significance. The decline in distal zone epicardial flow also was responsible for the statistically significant increase in the distal zone endocardial/epicardial blood flow ratio observed during arterial counterpulsation. In response to balloon pumping, the relative change versus control in blood flow in both distal zone endocardium (decline to 95.9 ± 8.6 % of control blood flow) and epicardium (89.8 ± 18.5 %) did not differ significantly from that of respective changes in blood flow in circumflex zone endocardium (90.0 ± 18.1 %) and epicardium (89.5 ± 19.0 %). A significant increase (versus levels during balloon pumping) in epicardial flow in both distal and circumflex zones was observed after discontinuation of arterial counterpulsation. Endocardial blood flow in both zones also tended to increase (versus levels during balloon pumping) after discontinuation of arterial counterpulsation although the changes failed to attain statistical significance.

TABLE II Regional Myocardial Blood Flow Response (ml·mn^{-1}·g^{-1}, Mean ± 1 SD) to Intraaortic Balloon Pumping (IABP) in 9 Pigs With a Severe Coronary Artery Stenosis

	Control I	IABP	Control II
Distal zone			
Endocardium	1.04 ± 0.20*	1.00 ± 0.24	1.10 ± 0.20
Epicardium	1.16 ± 0.36*	1.01 ± 0.27†	1.20 ± 0.24‡
Endo/epi ratio	0.92 ± 0.12*	1.00 ± 0.09†	0.93 ± 0.09
Circumflex zone			
Endocardium	1.67 ± 0.77	1.44 ± 0.47	1.80 ± 0.44
Epicardium	1.48 ± 0.60	1.27 ± 0.37	1.59 ± 0.36‡
Endo/epi ratio	1.12 ± 0.10	1.13 ± 0.09	1.13 ± 0.08
Distal/circumflex zone flow ratio			
Endocardium	0.67 ± 0.14	0.72 ± 0.10	0.63 ± 0.09
Epicardium	0.81 ± 0.06	0.81 ± 0.07	0.76 ± 0.06

* $p < 0.01$ versus circumflex zone (control I). † $p < 0.05$ versus control I. ‡ $p < 0.05$ versus IABP.
Endo/epi = endocardial/epicardial.

Regional (distal zone) myocardial oxygen metabolism (Table III; Fig. 3): Two animals were omitted from analysis because it was not possible to properly position the anterior interventricular vein catheter. Intraaortic balloon pumping resulted in significant decreases (versus control) in the arterial-anterior in-

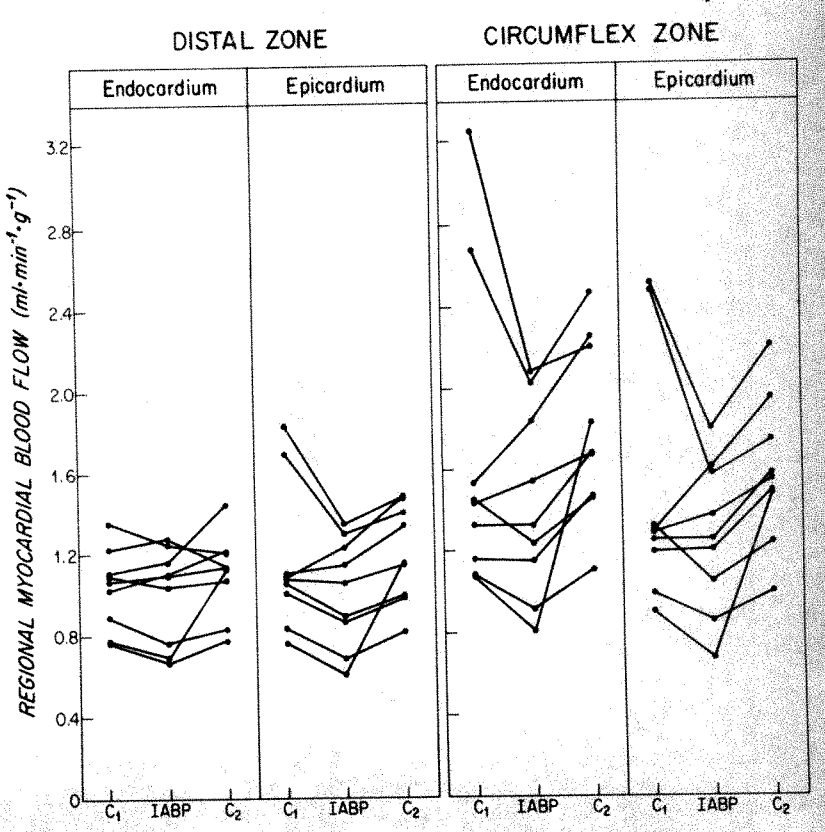

FIGURE 2. Individual responses to intraaortic balloon pumping (IABP) of distal and circumflex zone endocardial and epicardial blood flow (microsphere technique) for each of the 9 animals. Note that in response to IABP distal zone endocardial and epicardial blood flow either failed to increase substantially or else declined in all animals. The response of the circumflex zone was similar for both endocardium and epicardium. Discontinuation of balloon pumping was associated with an increase (versus levels during IABP) in blood flow in both endocardium and epicardium in both zones in all but 2 animals in which distal zone endocardial flow declined modestly after counterpulsation was stopped. C_1 and C_2 = control 1 and control 2 periods, respectively.

TABLE III Regional (Distal Zone) Myocardial Oxygen Metabolism: Results (Mean ± 1 SD) of Intraaortic Balloon Pumping (IABP) in 7 Pigs With a Severe Coronary Artery Stenosis

	Control I	IABP	Control II
Arterial oxygen content (vol/100 ml)	13.22 ± 1.08	12.41 ± 1.10*	12.08 ± 1.05*
AIV oxygen content (vol/100 ml)	1.46 ± 0.43	1.71 ± 0.66†	1.46 ± 0.64
Arterial-AIV oxygen difference (vol/100 ml)	11.76 ± 1.15	10.70 ± 1.22*	10.62 ± 0.93*
Regional myocardial oxygen extraction (%)	88.8 ± 3.7	86.2 ± 5.3†	88.0 ± 5.0
Regional myocardial oxygen consumption (ml·min^{-1}·100 g)	12.95 ± 3.55	10.26 ± 2.52†	11.72 ± 1.84

* $p < 0.01$ versus control I. † $p < 0.05$ versus control I.
AIV = anterior interventricular vein.

terventricular vein oxygen difference, myocardial oxygen extraction, and oxygen consumption in the distal zone. After discontinuation of arterial counterpulsation, regional myocardial oxygen extraction and consumption both returned to values that did not differ significantly from those of control I. Finally, it should be noted that a strong linear correlation was observed between the rate-pressure product and distal zone regional myocardial oxygen consumption ($r = 0.74$, $p < 0.002$; pooled data consisting of 2 observations, control and intraaortic balloon pumping, in each of 7 animals).

Group II (Additional Animals) (n = 5)

Effects of insertion of the artificial stenosis on regional myocardial blood flow and function (n = 2 animals) (Table IV): In both animals changes in mean arterial pressure and heart rate were small (versus prestenosis control) after placement of the stenosis. In both animals prestenosis endocardial flows expressed as the ratio distal/circumflex flow declined 10 minutes after placement of the stenosis and remained at similar levels 30 minutes after placement. Also, the absolute value of endocardial flow in the distal zone declined (versus prestenosis control) in both animals after insertion of the stenosis. In the epicardial region the control flow ratio declined in both animals at 10 minutes after placement of the stenosis as did the absolute values of distal zone epicardial flows. Thirty minutes after placement, the distal/circumflex epicardial flow ratio remained depressed in 1 animal but returned to control levels in the other. Regional systolic function measured by mean velocity of circumferential fiber shortening (fractional shortening/ejection time) was depressed (versus control) in the distal zone at 10 and 30 minutes after placement of the stenosis in both animals. Thus, in both animals the stenosis caused a reduction in regional endocardial blood flow as well as evidence of impaired systolic function. Although epicardial blood flow declined only slightly after placement of the stenosis in the distal zone of these 2 animals, in the primary series (n = 9) the distal/circumflex epicardial flow ratio (0.81 ± 0.06) was less than that of the left anterior descending/circumflex epicardial flow ratio of 63 normal

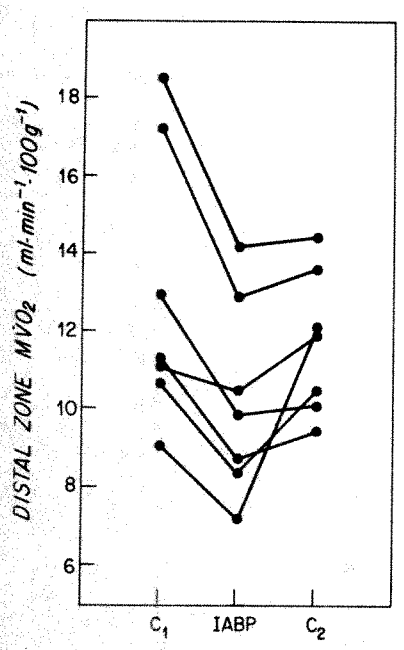

FIGURE 3. Individual responses to balloon pumping (IABP) of distal zone regional myocardial oxygen consumption (MVO_2) for each of the 9 animals. A decline in MVO_2 in response to IABP occurred in each animal. C_1 and C_2 = control 1 and control 2 periods, respectively; MVO_2 = (arterial − anterior interventricular vein O_2 content difference) × (transmural distal zone blood flow).

TABLE IV Regional Blood Flow and Systolic Function (Distal/Circumflex Ratio) Before and After Insertion of the Artificial Stenosis*

			Distal/Circumflex Ratio		
Group II Animal	HR	MAP	Endo Flow	Epi Flow	Mean Vcf
Prestenosis Control					
1	111	101	1.00	0.98	1.15
2	137	108	0.91	0.79	0.85
10 Minutes After Stenosis					
1	111	96	0.46	0.94	0.48
2	148	105	0.73	0.73	0.67
30 Minutes After Stenosis					
1	113	94	0.42	0.95	0.50
2	134	104	0.80	0.80	0.75

* Blood flow and regional function data are expressed as the ratio of absolute values distal/circumflex zone.
Endo = endocardial; Epi=epicardial; HR = heart rate; MAP = mean arterial pressure; Vcf = velocity circumferential fiber shortening.

TABLE V Effect of Intraaortic Balloon Counterpulsation on Distal Zone Myocardial Blood Flow and Function (3 Animals With a Severe Coronary Stenosis)

Group II Animal	Distal Zone Regional Myocardial Blood Flow ($ml \cdot min^{-1} \cdot g^{-1}$)				Distal Zone Regional Systolic Function		Distal Zone Regional Oxygen Consumption ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)		Rate Pressure Product ($mm\ Hg \cdot min^{-1}$)	
	Control		IABP							
	Endo	Epi	Endo	Epi	Control Mean Vcf	IABP Mean Vcf	Control	IABP	Control	IABP
3	0.44	1.17	0.70	0.79	0.37	0.45	7.98	7.13	13,888	9,180
4	1.25	0.95	0.96	0.72	0.25	0.26	10.08	8.65	9,370	7,371
5	0.75	0.64	0.61	0.30	0.37	0.46	7.90	5.69	10,492	7,900

Endo = endocardium; Epi = epicardium; IABP = intraaortic balloon pumping; Vcf = velocity circumferential fiber shortening (s^{-1}).

pigs (1.02 ± 0.09, $p < 0.001$) studied under similar conditions in our laboratory in the course of other experiments (unpublished observations).

Effects of intraaortic balloon counterpulsation on regional myocardial function (n = 3) animals with severe coronary artery stenosis) (Table V): Mean velocity of circumferential fiber shortening improved versus control during balloon pumping in 2 of the 3 animals and remained unchanged in the 3rd. Each animal demonstrated a reduction (versus control) in both rate pressure product and regional myocardial oxygen consumption in response to arterial counterpulsation. Similarly, epicardial blood flow distal to the stenosis declined versus control during arterial counterpulsation in each animal. Distal zone endocardial blood flow also declined versus control during balloon pumping in animals but improved in the 3rd. Circumflex zone endocardial and epicardial flows declined versus control in each animal in response to balloon pumping. Regional systolic function improved versus control in the circumflex zone in response to counterpulsation in 2 animals. Circumflex zone function could not be determined in the 3rd animal because the length sensors in this region failed to function properly at the time of the study.

Discussion

Critique of methods: For the preparation to be useful in understanding the mechanism by which arterial counterpulsation ameliorates myocardial ischemia in the setting of a severely stenosed but patent coronary artery, it is necessary to establish that regional ischemia was present distal to the stenosis. In this regard data obtained in 2 animals in which regional flow and function were measured before and after insertion of the stenosis demonstrated that the stenosis caused a decline in regional blood flow and impairment of regional systolic function, that is, functional evidence of ischemia. Furthermore, studies by other investigators[24,25] show that even modest decreases in regional subendocardial blood flow are capable of impairing endocardial as well as epicardial fiber shortening and hence causing functional evidence of ischemia. In the primary group of 9 animals used in this study the distal zone endocardial/epicardial flow ratio was less than unity and significantly less than that of the circumflex zone. Moreover, the absolute value of the distal zone endocardial/epicardial ratio under control condition (0.92 ± 0.12) undoubtedly would have been lower if we had sectioned the hearts into 4 layers and compared the innermost endocardial layer with the outermost epicardial layer as other investigators have done.[24,26] In addition, distal zone endocardial flow was reduced to a mean of 67% of circumflex zone endocardial flow under control conditions whereas distal zone epicardial flow was reduced to a mean of 81% of circumflex zone epicardial flow (Table II). Accordingly, it is clear at a minimum that the distal zone endocardium was underperfused at rest in the primary group of 9 animals used in the study.

It is reasonable to assume that regional myocardial ischemia (manifested by impaired systolic function) also was present because (1) hypoperfusion of the endocardium is known to impair regional function, and (2) studies in the smaller group of 2 animals demonstrated deterioration of regional function after placement of the stenosis. In addition, it should be recalled that most patients with unstable angina pectoris usually manifest subendocardial rather than transmural myocardial ischemia,[1–4] an observation that also supports the relevance of the animal model used in this study to the clinical problem of unstable angina pectoris in man. Finally, it should be emphasized that the model employed may not be relevant to the patient with myocardial ischemia complicated by cardiogenic shock. Intraaortic balloon pumping may relieve ischemia and improve ventricular performance in such patients by a different mechanism (such as an increase in coronary perfusion pressure with a subsequent increase in myocardial blood flow[5]) from that which applies to patients with ischemia but normal arterial pressure and cardiac output (see later).

Analysis of results: The purpose of this study was to determine the effect of intraaortic balloon pumping on regional myocardial blood flow distal to a severe coronary artery stenosis. Experiments were performed in a controlled, closed chest, conscious animal model with at least moderate regional ischemia in order to better understand the mechanism(s) by which this intervention ameliorates myocardial ischemia in patients with unstable angina pectoris. We observed that arterial

TABLE VI Distal Zone Endocardial and Epicardial Blood Flow Response to Intraaortic Balloon Pumping (IABP): 5 Animals in Which Distal Coronary Mean Diastolic Pressure Increased During IABP

Group I Animal	Distal Mean Diastolic Pressure (mm Hg)		Rate Pressure Product (mm·Hg·min^{-1})		Endocardial Blood Flow (ml·min^{-1}·g^{-1})		Epicardial Blood Flow (ml·min^{-1}·g^{-1})		Myocardial Oxygen Consumption (ml·min^{-1}·100 g^{-1})	
	Control	IABP	Control	IABP	Control	IABP	Control	IABP	Control	IABP
2	56.9	65.9	8,333	7,455	0.76	0.66	0.83	0.68	11.16	8.74
4	52.6	60.8	9,060	8,520	1.07	1.09	1.08	1.06	9.83	8.67
5	84.4	102.9	8,528	7,718	0.78	0.69	0.76	0.61	9.07	7.16
8	56.0	68.0	14,070	12,470	1.23	1.28	1.83	1.35	. . .*	. . .*
9	71.9	83.1	8,928	7,761	0.89	0.76	1.00	0.86	10.74	8.43
Mean	64.4	76.1	9,784	8,785	0.95	0.90	1.10	0.91	10.20	8.25
SD	13.4	17.1	2,414	2,098	0.20	0.27	0.43	0.30	0.94	0.74

* The anterior interventricular vein catheter could not be selectively positioned in this animal; hence MVO_2 data are unavailable.

counterpulsation produced a consistent reduction in tension time index and rate pressure product along with a significant increase in mean diastolic pressure in the aorta. The magnitude of these changes was comparable to those achieved by previous investigators in studies conducted in both canine preparations[5–8,15] and man.[3,4] Despite the fact that aortic mean diastolic pressure was successfully augmented by arterial counterpulsation, no change in mean diastolic or overall mean distal coronary artery pressure occurred for the primary group as a whole (n = 9) although 5 of 9 animals did exhibit an increase in mean diastolic pressure distal to the stenosis. Likewise, myocardial blood flow distal to the stenosis was not increased by balloon pumping. Indeed, epicardial blood flow declined significantly distal to the stenosis. Furthermore, a strong correlation was observed between the rate pressure product and regional myocardial oxygen consumption distal to the stenosis. Thus, the distal coronary bed appeared to autoregulate in response to a decrease in myocardial oxygen demand. Accordingly, distal zone blood flow failed to increase with balloon pumping not only because distal coronary pressure failed to increase in some cases but also because autoregulation of the distal coronary bed occurred.

Analysis of distal zone endocardial and epicardial blood flow responses to balloon pumping in the 5 animals in which an increase in distal coronary mean diastolic pressure occurred supports the hypothesis that autoregulation of blood flow occurred in the distal zone. Thus, an actual decrease in endocardial blood flow was observed during balloon pumping in 3 of these animals (Table VI) despite the increase in distal coronary mean diastolic pressure in all. The increments (versus control) in endocardial blood flow in 2 of the animals (2 and 4%, respectively) were small in comparison with the associated increments in distal mean diastolic pressure (16 and 21%, respectively). Furthermore, in all 5 animals distal zone epicardial blood flow decreased (versus control levels) during arterial counterpulsation. Finally, oxygen extraction by the myocardium distal to the stenosis declined in response to arterial counterpulsation (Table III), an observation that also supports the hypothesis that the distal zone autoregulated its blood flow in response to a reduction in myocardial oxygen demand.

We recognize that a decline in myocardial blood flow and oxygen consumption in the distal zone during arterial counterpulsation could just as well have been caused by a deterioration in regional myocardial function or a decrease in contractility, or both. A reflexly mediated decline in myocardial contractility occurs in dogs during balloon pumping.[7,8] However, because reflex withdrawal of sympathetic tone is thought to underly this response to arterial counterpulsation,[8] this mechanism is probably not applicable to the present study because all animals were pretreated with propranolol (1 to 2 mg·kg^{-1}) before institution of balloon pumping. It also should be noted that the reduction in maximal positive left ventricular dP/dT observed during arterial counterpulsation may simply reflect the associated decrease in left ventricular systolic pressure[27] and does not necessarily imply a decline in contractility. A deterioration in regional myocardial function with arterial counterpulsation also seems unlikely because studies in animals[28] and man[2] indicate that balloon pumping improves regional function in ischemic (as opposed to infarcted) myocardium.

In the present study balloon counterpulsation also improved regional systolic function in the 3 animals studied with ultrasonic length sensors. A decline in regional myocardial oxygen consumption during balloon pumping was measured in each of these 3 animals. Because the bulk of oxygen used by the working heart is consumed in the generation of tension with relatively little additional cost accruing to fiber shortening,[29] it is quite possible that function (defined as fiber shortening) could improve at the same time that oxygen consumption declines if afterload also is reduced (as it is with balloon pumping). Accordingly, the most likely explanation for the observed tendency for blood flow and oxygen consumption to decline in response to arterial counterpulsation is related to the tendency of the distal zone to autoregulate its blood flow in response to a reduction in oxygen demand. However, it should be emphasized that the reduction in myocardial oxygen

demand is most likely caused by systolic unloading of the ventricle rather than by depression of contractility or impairment of systolic function.

Implications: The results of this investigation demonstrate that arterial counterpulsation effectively reduces myocardial oxygen demand by means of afterload reduction but generally does not improve myocardial blood flow distal to a severe coronary stenosis. Failure of balloon pumping to increase regional blood flow distal to a severe stenosis is probably the result of (1) failure in some cases to augment mean diastolic pressure distal to the stenosis, and (2) the tendency of the distal coronary circulation to exhibit autoregulation in response to a reduction in myocardial oxygen demand. Accordingly, the data support the hypothesis that arterial counterpulsation ameliorates myocardial ischemia in the setting of a severely stenosed but patent coronary artery primarily by reducing myocardial oxygen demand rather than by increasing oxygen supply.

Acknowledgment

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Detection of Ischemic Myocardium in Vivo Through the Chest Wall By Quantitative Ultrasonic Tissue Characterization

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Quantitative analysis of ultrasound offers a potentially valuable method for noninvasive differentiation of specific types of cardiac disease and for assessment of their severity. Clinical application necessitates quantitative measurement of the ultrasonic properties of myocardium through the chest wall. This study was designed to determine whether such measurements could be made noninvasively with the aid of conventional M mode echocardiographic guidance and to characterize the quantitative effects of intervening tissue (chest wall) on the ultrasonic signals backscattered by ischemic and normal myocardium. Frequency-dependent ultrasonic backscatter (2 to 7 MHz) from normal myocardium was measured in dogs in vivo through the closed chest with the use of M mode guidance and with the chest open, directly from the myocardium. Closed-chest and open-chest measurements were repeated after ligation of the left anterior descending coronary artery in the same animals. Closed-chest data were compensated by correcting for the average value for the slope of the attenuation-frequency function of chest wall, which was determined from measurements obtained by analysis on excised tissue. Compensated closed-chest measurements correlated with measurements obtained from the epicardial surface of the heart. The differentiation of normal from ischemic myocardium with both the closed- and open-chest measurements was consistent ($p < 0.005$). The successful differentiation of normal from ischemic myocardium by determination of quantitative backscatter through the intervening chest wall supports the concept that tissue characterization by quantitative analysis of backscattered ultrasound is a potentially useful, clinically applicable approach to noninvasive detection and differentiation of intrinsic properties of normal and diseased myocardium.

Characterization of tissue based on the quantitative analysis of its ultrasonic properties is a rapidly evolving area of echocardiography. Previous reports from our own and other laboratories[1-6] indicate that ultrasonic attenuation and backscatter are two variables with particular promise. For example, attenuation of transmitted ultrasound in vitro was found to correlate closely with myocardial ischemic injury quantified by creatine kinase depletion.

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Backscatter represents ultrasonic energy reflected as the result of interactions within the tissue. It is widely employed in a qualitative fashion in clinical ultrasonic imaging systems.[7-10] In vitro, quantitative measurements of ultrasonic backscatter are significantly altered by myocardial infarction due to influences of edema formation, intravascular blood cell elements, and collagen deposition.[5,11] Cardiomyopathic changes such as those induced by doxorubicin also influence quantitative ultrasonic backscatter measured in vitro.[12] Thus, quantitative analysis of ultrasonic backscatter may permit characterization of intrinsic properties of tissue in vivo with reflected ultrasound.

Previous experiments from our laboratory have involved analysis of excised canine myocardium, isolated perfused rabbit hearts, and open-chest dogs. The time course of increases in backscatter accompanying acute myocardial infarction was measured quantitatively in

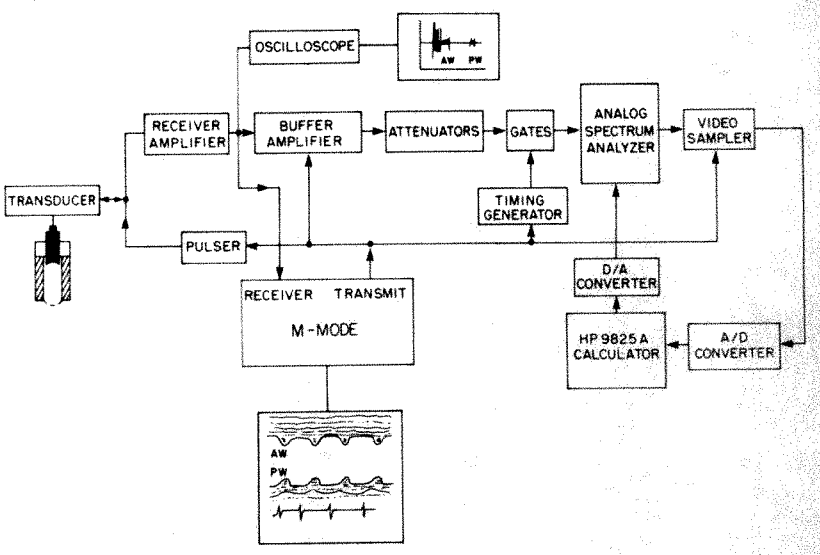

FIGURE 1. Block diagram of the data acquisition system.

an open-chest animal preparation.[5] However, clinical applications of ultrasonic tissue characterization require noninvasive measurements of ultrasound through the closed-chest wall. Unfortunately, the frequency-dependent attenuation of ultrasound by the chest wall represents a formidable obstacle to quantitative analysis of backscatter from the heart in vivo.

This study was undertaken to develop and evaluate an approach to measurement of myocardial backscatter noninvasively with the use of echocardiographic M mode guidance and to determine whether measurements of myocardial backscatter obtained from the epicardial surface of the heart in situ correlate with those obtained through the closed-chest wall in vivo when the latter are compensated for chest wall attenuation. Results indicate that myocardial backscatter can be quantified in the intact dog and used to differentiate myocardium exhibiting altered intrinsic ultrasonic properties induced by ischemia from normal tissue.

Methods

Animal preparations: Mongrel dogs were anesthetized with sodium thiopental, intubated, and ventilated with 100% oxygen and halothane. The left chest wall was shaved to provide improved transducer contact. A Smith Kline and French Ekoline M mode echocardiograph was used for guidance and to provide an electrocardiographic signal obtained with subcutaneous needle electrodes. Traditional M mode echocardiographic techniques were used for spatial localization, and quantitative analysis of ultrasound was performed on the tissue in the region of interest. The transducer with its M mode and backscatter electronics connected in parallel was placed on the surface of the skin of the left chest wall in the area of the maximal visible impulse. The transducer housing was held in position by a clamp mounted to the dog harness to prevent movement during data collection. To collect ultrasonic signals perpendicular to the myocardium and in contiguous areas, a careful search was made for sites that produced a distinct and persistent specular reflection from the endocardial surface. This practice also aided in accurate placement of the backscatter window within the boundaries of the myocardium. The M mode image was displayed on a Smith Kline and French printer as simultaneous collection of the backscattered data proceeded from multiple sites within a zone of the free wall of the left ventricle.

Acoustic windows were small in some animals, and the overall availability of sites varied from animal to animal. Separate sites were defined by a change in transducer position or orientation, resulting in an observed difference in wall motion pattern with maintenance of a distinct specular reflection from the endocardial surface. Because the beam width was narrow (approximately 3 mm in the focal zone), only minute movements of the transducer were necessary to characterize each new site.

For comparison with measurements obtained through the chest wall, additional data were collected with the transducer coupled directly to the epicardial surface. A right thoracotomy incision was made in the 5th intercostal space, the heart was suspended in a pericardial cradle, and backscatter measurements were taken from the area of the left ventricle adjacent to the left chest wall which comprised myocardium supplied by the left anterior descending coronary artery (LAD). Subsequently, lidocaine was administered as a 100 mg bolus to diminish ventricular arrhythmia, and the LAD was ligated immediately distal to the 1st diagonal branch. Two to 4 hours later backscatter measurements were taken from multiple sites within the ischemic region with the transducer coupled directly to the epicardial surface. The pericardium was then partially closed, and the right thoracotomy incision was repaired surgically. The dog was again suspended in the harness. Repeat measurements were obtained noninvasively from the untouched left chest wall with the use of M mode guidance as previously described. The ischemic zone was readily detectable based on hypokinesia or akinesia.

Ultrasonic methods: A block diagram of the data acquisition system is shown in Figure 1. The transmit pulse from a conventional M mode unit was used to trigger a separate pulser and all timing circuits. The pulser (Metrotek model MP 215) sent a short (less than 500 ns), high voltage impulse to a broadband transducer (Panametrics V309, 1.2 cm diameter, 5 MHz center frequency, and 5 cm focal length) which produced an ultrasonic pulse of wide bandwidth.

The transducer was mounted in a Plexiglas holder which was filled with degassed, distilled water and capped by a flexible latex tip. The water column served as an acoustic delay line and facilitated placement of the tissue of interest within the focal zone of the transducer. Closed-chest measurements were made with the tip placed against the skin after applica-

tion of acoustic gel. Open-chest measurements were taken with the tip applied directly to the epicardial surface.

The backscattered signal was amplified (Metrotek MR 101, 40 dB nominal gain) and then split with 1 portion returning to the M mode receiver port. The other portion of the signal was buffered, and a 4 to 6 μs portion of the signal arising from the anterior wall was gated into an analog spectrum analyzer. The center frequency of the spectrum analyzer was under computer control and swept from 2 to 7 MHz in 500 kHz steps (analyzer bandwidth 300 kHz).

The spectrum analyzer output was integrated with a 30 μs time-constant to sum over the entire gate, and then sampled and fed into an analog to digital converter. The computer (Hewlett-Packard 9825A) sampled the converted signal at a single frequency 200 times over 2 seconds and averaged all values to encompass several heart cycles before setting the analyzer to the next frequency. Raw data spectra were recorded on magnetic tape for subsequent processing. Simultaneous M mode recordings were made and chest wall thickness was estimated from the M mode and radio frequency (RF) tracing.

Immediately after completion of data collection the transducer was immersed in a degassed water bath and a planar stainless steel reflector (employed for calibration) placed at a distance corresponding to that of the tissue analyzed previously. Reference spectra with selected amounts of electronic attenuation were recorded for calibration purposes. During processing, the data spectra were compared with the reference values, and the spectra were reduced to signal magnitude relative to the reflector expressed in decibels (dB).

The chest wall attenuation data were collected from a separate set of animals with the use of a minicomputer-based acquisition and analysis system. Specimens of chest wall were sutured to a Plexiglas holder and immersed in a bath of degassed sodium citrate solution at a normal osmotic concentration. Narrow band pulses of 4 μs duration with center frequencies under computer control over the range 3 to 6.5 MHz were launched from a commercial wideband piezoelectric transducer (Panametrics V309, 5 MHz center frequency, 0.5 inch diameter, and 10 cm focal length) and were received with an acoustoelectric receiver, constructed in our laboratory to avoid phase cancellation errors (aperture 1.2 cm^2).[13,14] Substitution measurements were obtained, and the signal strength, as a function of frequency, was computed. The average slope of the attenuation ($\overline{\alpha_I}$) as a function of frequency was found to be 1.8 ± 0.4 dB/cm/MHz (mean ± standard deviation, 5 dogs, 111 sites).

The backscatter transfer function of a tissue is represented as S(f), a function of the frequency (f). If this tissue is insonified through an intervening layer of thickness D and attenuation coefficient $\alpha_I(f)$, then the ultrasonic intensity received by the transducer in a pulse echo experiment is

$$V_{tissue}(f) = P(f)S(f)e^{-2D\alpha_I(f)} \quad (1)$$

where P(f) is the spectrum of the incident pulse and the response of the electronic system. If the tissue is replaced by a planar, nearly perfect reflector, a reference signal is obtained:

$$V_{ref} = P(f) \quad (2)$$

Dividing $V_{tissue}(f)$ by $V_{ref}(f)$ yields the relative spectrum:

$$V(f) = S(f)e^{-2D\alpha(f)} \quad (3)$$

(In open-chest measurements D = 0, and thus the transfer function S(f) is obtained directly.)

In each experiment spectra were obtained from different sites and averaged. At each site the chest wall thickness D was estimated echocardiographically. The individual estimates were used to obtain an average thickness ($\overline{D}$) for each animal. This estimate of thickness and the average attenuation coefficient measured as described above, $\overline{\alpha_I(f)}$, were used to obtain a compensation factor $e^{2\overline{D}\overline{\alpha_I(f)}}$ for each animal. Thus, closed-chest spectra were compensated for the frequency-dependent attenuation of chest wall to obtain an estimate, $S_{est}(f)$, of the backscatter transfer function of myocardium:

$$S_{est}(f) = S(f)\, e^{-2D\alpha_I(f)}e^{2\overline{D}\overline{\alpha_I(f)}} \approx S(f) \quad (4)$$

Statistical methods: Comparison of data from open- and closed-chest conditions was performed with chi-square analysis. Separation of normal and ischemic myocardium was evaluated with student's t test.

Results

Upright positioning of the animals proved to provide the most consistent and repeatable echocardiograms. Only animals from whom pre- and postinfarct echoes could be obtained are reported. Some of the problems leading to failure to obtain both sets of measurements in other dogs included anesthesia- or ligation-induced arrhythmias including ventricular fibrillation and lung interposition blocking acoustic windows.

Contraction of the anterior wall detectable by echocardiography was angle-dependent before and after coronary artery ligation. Diminished wall motion may have been due to halothane, along with the bradycardia often seen. However, neither altered wall motion nor systolic wall thinning hampered the placement of the backscatter gate, because gate position was dependent on the location of the specular reflection from the endocardial surface. The specular reflection was used to assure approximately perpendicular orientation of the tissue to the insonifying beam.

Representative samples of M mode echocardiograms from normal and ischemic myocardium are shown in Figure 2. The top panel displays wall motion of normal, anterior left ventricular myocardium. The bottom panel illustrates lack of motion of the anterior wall induced by ischemia. The ischemic anterior wall akinesia, compensatory increased motion of the posterior wall, and the observed electrocardiographic changes are consistent with myocardial infarction.

Figure 3 displays the average backscatter from normal myocardium in 5 dogs as a function of frequency from 2 to 7 MHz. The magnitude is displayed in dB relative to the reflections from a stainless steel reflector, the standard by which all signals were calibrated. The top panel of Figure 3 depicts measurements with open- and closed-chest conditions without compensation for chest wall attenuation. The frequency-dependent differences between these 2 spectra are caused by attenuation of the chest wall. The bottom panel of Figure 3 shows virtual superimposition of results when closed-chest measurements were compensated for chest wall attenuation. Figure 4 shows comparable results from ischemic myocardium in the same 5 animals. The measurements obtained under closed- and open-chest conditions correspond closely when the closed-chest

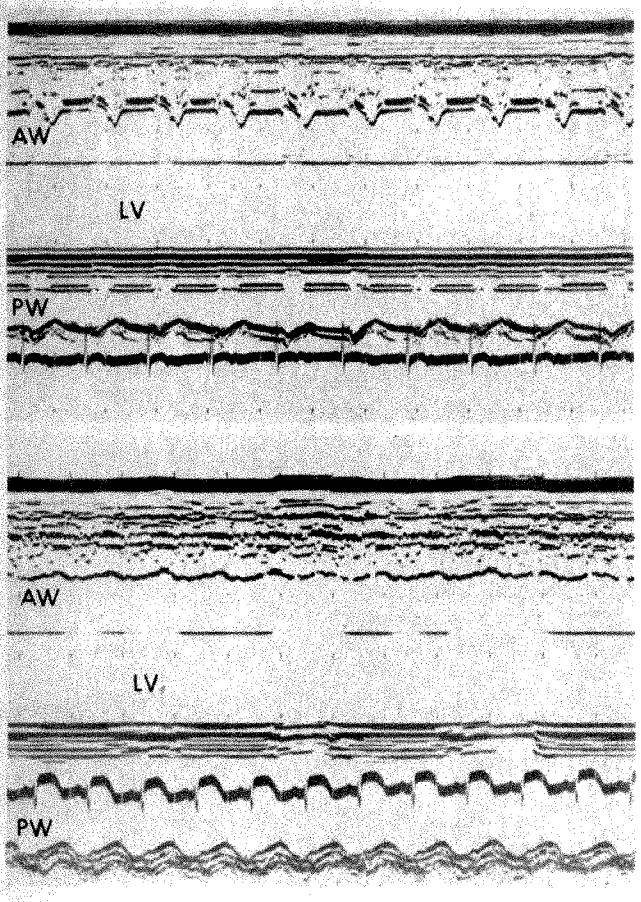

FIGURE 2. M mode electrocardiograms displaying normal anterior wall (AW) motion (**top panel**) and diminished anterior wall motion resulting from coronary artery ligation (**bottom panel**). PW = posterior wall; LV = left ventricle.

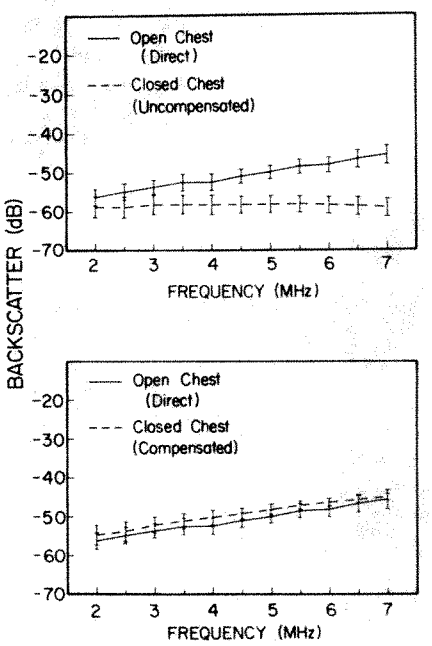

FIGURE 3. Backscatter as a function of frequency obtained from normal canine myocardium under open- and closed-chest conditions without compensation for chest wall attenuation (n = 5 dogs) (**top panel**). Corresponding data with closed-chest values compensated based on chest wall attenuation (**bottom panel**).

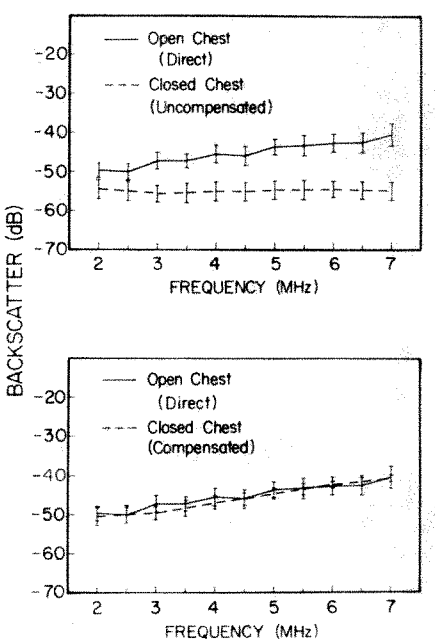

FIGURE 4. Backscatter as a function of frequency obtained from ischemic canine myocardium under open- and closed-chest conditions without compensation for chest wall attenuation (n = 5 dogs) (**top panel**). Corresponding data with closed-chest values compensated based on chest wall attenuation (**bottom panel**).

measurements are compensated for the attenuation of chest wall. The measurements from ischemic tissue demonstrate increased backscatter in comparison with results from normal zones.

In Figure 5, the closed-chest estimates of backscatter are correlated with the open-chest measurements at the same frequency and from the same animals with a line of identity shown for reference. In the top panel, the uncompensated backscatter values fall below the line of identity ($\chi^2 = 8.33$, n = 5 dogs, 55 data points). In the bottom panel, which depicts results after compensation for chest wall attenuation, values distribute well along the line of identity ($\chi^2 = 0.77$). Similar results from ischemic myocardium are shown in Figure 6, with corresponding values of $\chi^2 = 12.05$ and 1.06 (n = 5 dogs, 55 data points) for uncompensated and compensated values, respectively.

The spectral data were averaged over frequency to obtain an index denoted integrated backscatter. In Figure 7, compensated closed-chest measurements are shown (normal −49.4 ± 0.34 dB, 90 sites; ischemic −45.8 ± 0.33 dB, 105 sites, mean ± standard error [SE], n = 5 dogs). These compensated values correlate with direct epicardial measurements (normal −50.8 ± 0.41 dB, 48 sites; ischemic −45.3 ± 0.46 dB, 48 sites, mean ± SE, n = 5 dogs). The separation of normal from ischemic myocardium for both the closed- and open-chest measurements was significant ($p < 0.005$) and comprised a difference in backscattered energy of more than 200%.

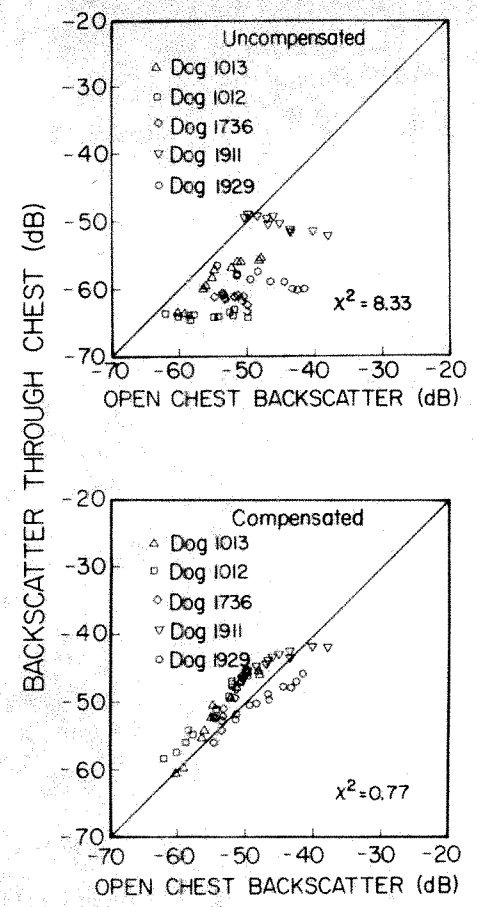

FIGURE 5. Uncompensated closed-chest backscatter from normal myocardium. The values fall substantially below a line of identity yielding a chi-square value of 8.33 **(top panel)**. Compensated closed-chest values compared with open-chest backscatter. The data fall along a line of identity, with chi-square = 0.77 **(bottom panel)**.

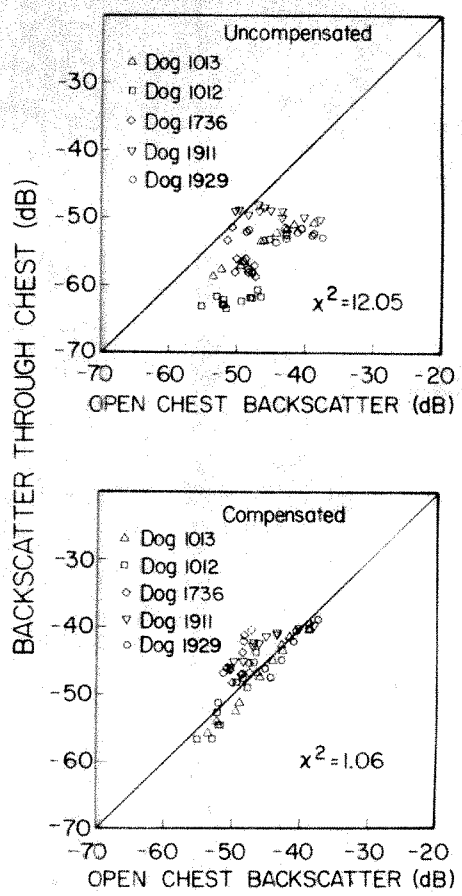

FIGURE 6. Uncompensated closed-chest backscatter from ischemic myocardium compared with open-chest backscatter. The values fall substantially below a line of identity yielding a chi-square value of 12.05 **(top panel)**. Compensated closed-chest values compared with open-chest backscatter. The data fall along a line of identity with chi-square = 1.06 **(bottom panel)**.

Discussion

Results from this study demonstrate that the quantitative analysis of ultrasonic backscatter permits noninvasive detection of myocardial structural alterations and intrinsic properties. Measurement of backscatter from normal and ischemic left ventricle through the closed chest were confirmed by open-chest data obtained from the heart in situ.

In previous studies we showed that ultrasound can be used to characterize physical properties of tissue in vitro. In zones of infarction analyzed in vitro with transmitted ultrasound, an ultrasonic index based on attenuation changed concordantly with an independent index of myocardial injury, creatine kinase depletion.[3] Subsequent experiments indicated that collagen content, measured by analysis for hydroxyproline, correlated closely with the ultrasonic index slope of attenuation with frequency.[15] Collagen deposition was found to contribute to the increased attenuation found in regions of completed myocardial infarction. In central dense regions of fibrosis associated with myocardial infarction in both dog and rabbit hearts, collagen deposition resulted in significantly increased ultrasonic backscatter.[11,15] Furthermore, perfusion of isolated rabbit hearts having zones of infarction with collagenase demonstrated that backscatter was sensitively dependent on intact collagen.[11]

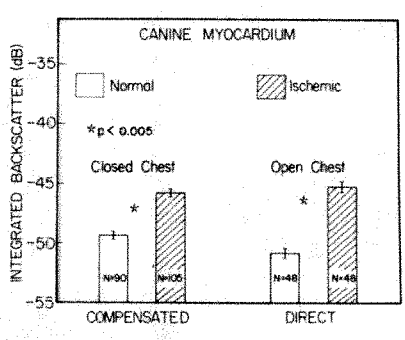

FIGURE 7. Integrated backscatter from normal and ischemic myocardium with compensated closed- and open-chest conditions ($p < 0.005$).

Backscatter was found to increase in acutely ischemic zones of open-chest dogs in vivo within 1 hour after the

onset of ischemia and to plateau at a value of 400% of control by 4 hours.[6] This increase in backscatter occurred only in regions of ischemic myocardium in which blood flow, measured with ^{141}Ce-labeled microspheres, was less than 20% of control. Thus, increased backscatter in acutely ischemic myocardium was not related linearly to flow. It appeared to depend on cellular and structural concomitants of severe ischemia. In additional experiments with perfused rabbit hearts, contributions of tissue water were implicated.[5]

The potential applicability of quantitative analysis of ultrasound for tissue characterization of the heart was explored further in vitro after induction of Adriamycin™ cardiomyopathy in rabbits. Integrated ultrasonic backscatter was increased in densely fibrotic regions and significantly, although less markedly, in myopathic regions without marked deposition of collagen.[12]

The present study was performed to determine whether the quantitative analysis of ultrasound obtained noninvasively could be used for tissue characterization in the intact dog. Difficulties in obtaining adequate acoustic windows are greater in dogs than in man, although the left ventricle in the dog is immediately adjacent to the chest wall whereas in man the right ventricle is interposed anteriorly. In many instances neither the epicardium of the anterior wall nor the posterior wall could be visualized readily. However, the identification of the specular reflection from the endocardium was found to be a useful landmark. When a large endocardial reflection was present, the gate for backscatter measurement could be placed so that it remained within the myocardium throughout the cardiac cycle. The spectral displays of Figures 3 and 4 show the separation of curves due to attenuation of the chest wall. The frequency dependence of the attenuation of the chest wall is evident from the greater separation of the curves at higher frequencies. The compensation factor, which also depends on chest wall thickness, showed only minor variation from animal to animal. The pericardium, even with associated fatty tissue, had insignificant effects on attenuation.

The spectral curves were converted to integrated backscatter by computing the area under the curve. Figure 7 shows the difference in integrated backscatter between normal and ischemic myocardium with closed- and open-chest measurements. Separation of values from ischemic and normal myocardium was slightly greater with the open-chest data probably because of factors influencing attenuation of sound by the intervening tissue, variability of chest wall thickness, and gate and focal zone position.

Despite these limitations, the present results suggest that myocardial acoustic properties can be quantified noninvasively and potentially clinically by adaptation of M mode and 2 dimensional echocardiographic techniques. Calculation of chest wall attenuation from reflected signals in real time will be necessary for studies in patients. Although attenuation is an intrinsic property of tissue, estimates obtained based on reflected ultrasound exhibit substantial variability. Aspects of the intervening tissue problem have been addressed by Reid[16] and others[17] who have considered several levels of required compensation and evaluated the advantages of generalized substitution techniques to yield both relative and absolute measurements. On the basis of previous results from our own and other laboratories[18] plus the experience gained in the studies reported here, clinically applicable methods for attenuation compensation in man appear to be quite feasible.

The diagnostic detection and differentiation of myocardial disease noninvasively based on quantitative ultrasonic characterization of tissue is a promising application of clinical ultrasonography. It may permit improved detection and differentiation of cardiomyopathies, cardiac tumors, and sequelae of ischemic events, as well as their responses to prophylactic or therapeutic interventions.

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Increased R-Wave Amplitude Induced by Acute Myocardial Ischemia in the Dog: A Predictor of Malignant Ventricular Arrhythmias

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The ability of an increase of 25% or greater in the sum of R-wave amplitudes in leads X, Y, Z, L_2, and V_5 to predict the occurrence of malignant ventricular arrhythmias (10 or more ventricular premature beats/min, ventricular tachycardia [5 or more consecutive premature beats], and/or fibrillation) was evaluated in 17 dogs during experimental acute myocardial ischemia. Each dog underwent a 15 minute ligation of the left anterior descending coronary artery followed by reperfusion and after recovery, 2 hours later, a 15 minute ligation of the circumflex coronary artery. During ligation of the left anterior descending coronary artery, 12 of 17 dogs (71%) showed no R-wave increase and no arrhythmias (true-negative response). In 5 (29%) of 17 dogs malignant ventricular arrhythmias developed: 2 of 5 (40%) dogs with arrhythmias had a concomitant R-wave increase (true-positive response), and 3 of 5 (60%) with arrhythmias had a less than 25% increase in R-wave amplitude (false-negative results). During circumflex coronary artery ligation, 13 of 17 (76%) dogs showed both R-wave increases and arrhythmias (true-positive response). Four (24%) of 17 dogs had no arrhythmias: 3 of 4 (75%) with no arrhythmias also had a less than 25% increase in R-wave amplitude (true-negative response), whereas 1 of 4 (25%) dogs with no arrhythmias had an increase in R-wave amplitude (false-positive response). In dogs with both arrhythmias and R-wave increases, R-wave changes preceded the onset of arrhythmias by a mean (± standard deviation) of 1 minute 27 seconds (±43 seconds). Overall, R-wave increases were highly sensitive (83%), specific (94%), and predictive (94%) for the occurrence of malignant ventricular arrhythmias during experimental acute myocardial ischemia.

R-wave amplitude increases have been observed in man during acute myocardial ischemia induced by both exercise and rapid atrial pacing.[1–9] Alterations in R-wave amplitude were also recorded in dogs after acute ligation of a major coronary artery[10] and may be seen as early as 10 seconds from the onset of ischemia.[11] After experimental canine coronary artery occlusion, changes in intramyocardial conduction were a major determinant of alterations in R-wave amplitude.[12] In other studies,[12–19] delays in intramyocardial conduction during the acute phase of myocardial ischemia were also closely associated with malignant ventricular arrhythmias. Conceivably, therefore, ischemia-induced alterations in R-wave amplitude might predict malignant ventricular arrhythmias. Thus, the present study was designed to determine the relation between R-wave amplitude alterations and the occurrence of malignant ventricular arrhythmias during the acute phase of experimental myocardial ischemia in a canine model.

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Methods

Seventeen healthy adult mongrel dogs (mean weight 16.5 ± 3.4 kg) were studied under pentobarbital sodium anesthesia (30 mg/kg body weight initially, with subsequent 1 to 2 mg/kg

TABLE I Correlation Between R-Wave Amplitude Changes and the Occurrence of Malignant Ventricular Arrhythmias During Acute Ischemia

	LAD Ligation (n = 17)				Cx Ligation (n = 17)			
	$\Sigma R\uparrow$	$\Sigma R_{L2,V5}\uparrow$	$\Sigma R\overrightarrow{\downarrow}$	$\Sigma R_{L2,V5}\overrightarrow{\downarrow}$	$\Sigma R\uparrow$	$\Sigma R_{L2,V5}\uparrow$	$\Sigma R\overrightarrow{\downarrow}$	$\Sigma R_{L2,V5}\overrightarrow{\downarrow}$
No malignant ventricular arrhythmias	0	0	12 (7.2 ± 2.1)	12 (6.3 ± 1.8)	1 (31.0)	1 (27.31)	3 (5.9 ± 1.7)	3 (6.1 ± 1.7)
Malignant ventricular arrhythmias	2 (29.3 ± 7.9)	2 (27.1 ± 8.3)	3 (15.1 ± 4.2)	3 (13.7 ± 4.3)	13 (41.3 ± 9.1)	13 (40.8 ± 10.2)	0	0

Numbers in parentheses indicate mean percentage change in R-wave amplitude from baseline ± standard deviation. Cx = circumflex coronary artery; LAD = left anterior descending coronary artery; $\Sigma R\uparrow$ = R-wave increase (25% or greater) in leads X, Y, Z, V_2, and V_5; $\Sigma R_{L2,V5}\uparrow$ = R-wave increase (25% or greater) in leads L_2 and V_5; $\Sigma R\overrightarrow{\downarrow}$ = R-wave increase 25% or less or R-wave decrease in leads X, Y, Z, L_2, and V_5; $\Sigma R_{L2,V5}\overrightarrow{\downarrow}$ = R-wave increase 25% or less or R-wave decrease in leads L_2 and V_5.

bolus infusions as indicated to maintain effective anesthesia). After intubation and ventilation with room air through a Harvard respirator, mid-sternotomy was performed, the pericardium opened, and the heart suspended in a pericardial cradle. The left anterior descending coronary artery was isolated approximately 1 to 3 cm beyond its origin from the left main stem, distal to the anterior septal artery and the first diagonal branch. Predictably, with our methods, occlusion at this site resulted in a relatively small area of ischemia in the canine myocardium. A snare ligature was placed around the artery for subsequent ligation. The left circumflex coronary artery was isolated approximately 1 to 2 cm from its origin and proximal to all branches, and a snare ligature was placed around the artery for subsequent ligation. Electrocardiographic leads L_2 and V_5 and Frank orthogonal leads X, Y, and Z were recorded throughout the experiment. The animal's limbs were restrained and their position was kept constant throughout the experiment to avoid electrocardiographic distortion related to positional changes.[20] The electrocardiogram was recorded by means of an 8 channel recorder (Hewlett Packard model 4578A) with the recording frequency set between 0.5 and 200 Hz. Data were also recorded continuously on an 8 channel FM tape recorder (Hewlett Packard model 3968A) for subsequent data reproduction and analysis.

Experimental protocol: In each dog, a 1 stage temporary (15 minute) ligation of the left anterior descending coronary artery was performed; release of the occlusion was followed by a 2 hour recovery period, after which a 1 stage temporary (15 minute) ligation of the left circumflex coronary artery was carried out, again followed by release of the occlusion. This sequence was chosen to enable us to perform both types of ligation in each dog. In preliminary studies the sequence of ligations was reversed (circumflex before left anterior descending coronary artery) in alternate animals. Although the results were similar, a large number of dogs were lost because of the high incidence of refractory ventricular fibrillation during circumflex coronary artery ligation, and therefore this protocol was abandoned.

In those animals in which ventricular fibrillation occurred during ligation of the left anterior descending artery, the artery was immediately reperfused and defibrillation accomplished with 1 or 2 countershocks of 10 and 40 W·s, respectively. After a 2 hour recovery period, the circumflex ligation procedure was performed.

Measurements and definitions: R-wave amplitude was measured from the P-R segment (zero level reference) to the peak of the R wave in leads L_2, V_5, X, and Y and to the nadir of the Q wave in lead Z. These measurements were performed at 15 second intervals throughout the ligation period starting 5 minutes before ligation. Each data point represented a mean of 10 consecutive beats to negate respiratory influences on R-wave amplitude. R-wave amplitudes were measured in all 5 recorded leads and summed arithmetically (ΣR). All R-wave amplitude data in the text and tables represent summed data. To facilitate clinical correlations the sum of the R waves in leads L_2 and V_5 ($\Sigma R_{L2,V5}$) was calculated separately and correlated with the sum of R wave amplitudes in all 5 leads. An increase of 25% in R-wave amplitude was regarded as a positive response, a change that could be discriminated reproducibly without significant intra- or interobserver variability.

On the basis of previous coronary occlusion studies in our laboratory, malignant ventricular arrhythmias were defined prospectively as the occurrence of 1 or more of the following: 10 or more ventricular premature beats/min, ventricular tachycardia (5 or more consecutive ventricular premature beats), and ventricular fibrillation. In analyzing our data, dogs classified as having "no malignant arrhythmias" had either no premature ventricular beats or only 1 to 2 premature beats/min.

Statistical analysis: To evaluate the sensitivity, specificity, and predictive value of the observations made in this study the following formulas were used[21]: Sensitivity = true positives/(true positives + false negatives) ×100; Specificity = true negatives/(true negatives + false positives) ×100; Predictive value = true positives/(true positives + false positives) ×100. All data presented in the text with respect to the time course of ventricular arrhythmias represent a mean ± standard deviation.

Results

Left anterior descending coronary artery ligations: No malignant ventricular arrhythmias were observed in 12 (71%) of the 17 dogs during the 15 minutes after ligation of the left anterior descending coronary artery (Table I). In each of these 12 animals (100%) the increases in both ΣR and $\Sigma R_{L2,V5}$ were less than 25% above baseline (true negatives, Fig. 1). In the remaining 5 of 17 dogs (29%) malignant ventricular arrhythmias (4 ventricular fibrillation, 1 ventricular tachycardia) occurred after ligation of the left anterior descending coronary artery. These arrhythmias occurred a mean of 6 minutes 17 seconds (±1 minute 37 seconds) after ligation. In 2 (40%) of these 5 dogs both ΣR as well as $\Sigma R_{L2,V5}$ increased more than 25% above baseline (true positives) and preceded the onset of malignant ventricular arrhythmias in both cases by a mean of 1 minute 18 seconds (±38 seconds). In 3 of 5 (60%) animals with

TABLE II Sensitivity, Specificity, and Predictive Value of R-Wave Amplitude Changes for the Occurrence of Malignant Ventricular Arrhythmias During Acute Ischemia

	Cx Ligation	LAD Ligation	Both Ligations
Sensitivity (%)	100	40	83
Specificity (%)	75	100	94
Predictive value (%)	93	100	94

Cx = circumflex coronary artery; LAD = left anterior descending coronary artery.

arrhythmias no significant changes (less than 25%) in either ΣR or $\Sigma R_{L2,V5}$ were observed (false negatives).

Left circumflex coronary artery ligations: Malignant ventricular arrhythmias were observed in 13 (76%) of 17 dogs after ligation of the left circumflex coronary artery (10 ventricular fibrillation, 2 ventricular tachycardia, and 1 frequent premature ventricular beats) (Table I). These arrhythmias occurred at a mean of 4 minutes 35 seconds (±2 minutes 15 seconds) after ligation. All 13 dogs (100%) with arrhythmias had an increase of 25% or greater in both ΣR and $\Sigma R_{L2,V5}$ (true positives) (Fig. 2). Increases in ΣR and $\Sigma R_{L2,V5}$ preceded the onset of malignant ventricular arrhythmias in each case, by a mean of 1 minute 37 seconds (±43 seconds). In 4 of 17 dogs (24%) no malignant ventricular arrhythmias occurred, and 3 (75%) of these 4 had less than 25% increases in both ΣR and $\Sigma R_{L2,V5}$ (true negatives), whereas in 1 dog (25%) both ΣR and $\Sigma R_{L2,V5}$ increased 25% or greater (false positive) (Table I).

Overall, an increase of 25% or greater in ΣR during the period of acute myocardial ischemia after left anterior descending coronary artery ligation showed a sensitivity of 40%, specificity of 100%, and a predictive value of 100% with respect to the occurrence of malignant ventricular arrhythmias (Table II). In comparison, an increase of 25% or greater in ΣR during circumflex ligation showed a sensitivity of 100%, specificity of 75%, and a predictive value of 93% with respect to the occurrence of acute malignant ventricular arrhythmias. When the data for both ligation procedures were combined, ΣR amplitude increases showed an overall sensitivity of 83%, specificity of 94%, and a predictive value of 94% in predicting the occurrence of acute ischemia-induced malignant ventricular arrhythmias. Results for $\Sigma R_{L2,V5}$ were identical to those for ΣR wave amplitude alterations with respect to sensitivity, specificity, and predictive value for malignant ventricular arrhythmias after both the left anterior descending and circumflex ligation procedures. In addition, $\Sigma R_{L2,V5}$ results were also concordant in each animal (Table II).

Discussion

R-wave amplitude increases have been observed in patients with acute myocardial ischemia induced by both exercise[1–8] and rapid atrial pacing.[9] R wave amplitude increases in the canine model of coronary artery occlusion have also been appreciated since the detailed observations of Rakita et al.[10] In experimental canine preparations, R-wave amplitude changes during acute, extensive myocardial ischemia follow a typical pattern.[11] There is an initial (onset within 10 seconds) and transient (duration 30 to 60 seconds) decrease in R-wave amplitude followed by a secondary marked and persistent increase in R-wave amplitude[11] (Fig. 2). In attempting to elucidate the pathophysiologic basis for this phenomenon, it was found that intramyocardial conduction changes rather than variations in intraven-

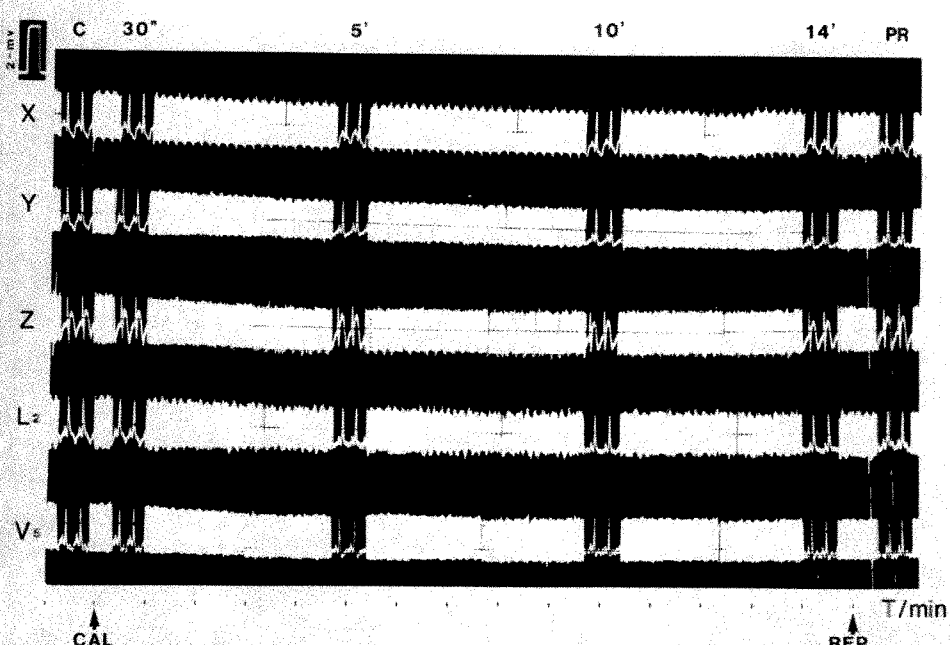

FIGURE 1. Electrocardiographic trend recording during ligation (CAL) and reperfusion (REP) of the distal left anterior descending coronary artery. Frank orthogonal leads X, Y, and Z as well as scalar leads L_2 and V_5 are demonstrated. Representative QRS complexes are shown during the control period (C), at 30 seconds, at 5, 10, and 14 minutes after coronary artery ligation, and in the immediate postreperfusion period (PR). Note that R-wave amplitude does not change significantly from control in any of these leads either after the 15 minute ligation period or during reperfusion. Correspondingly, this dog had no malignant ventricular arrhythmia.

tricular volume were the major factor determining R-wave amplitude changes during acute myocardial ischemia.[12] The initial decrease in R-wave amplitude was closely related to a transient shortening of intramyocardial conduction time (from endocardium to epicardium) observed during the first 30 to 60 seconds of acute myocardial ischemia, whereas the later and persistent increase in R-wave amplitude occurred in association with a marked delay in intramyocardial conduction.[12]

It is well established that malignant ventricular arrhythmias occur commonly during acute experimental myocardial ischemia, although their frequency is highly variable (10 to 90%).[21,22] The incidence of ventricular arrhythmias after coronary artery occlusion depends on many factors such as the vessel ligated, the method of occlusion (such as 1 stage versus 2 stage), and the site of occlusion (such as proximal versus distal); with the mass of tissue involved and the extent of preformed anastomosing collateral vessels as critical factors.[23] Previously, investigators have related the occurrence of malignant arrhythmias during acute ischemia to associated alterations and delays in local conduction.[13–19] Thus, on the basis of the association of both arrhythmias and R-wave amplitude changes with alterations in intramyocardial conduction it was of considerable interest to study the possible relation of arrhythmias and R-wave changes. Clinically, intramyocardial conduction changes cannot be measured directly. Therefore, the potential clinical importance of R-wave amplitude alterations as markers for subsequent malignant arrhythmias was considered.

The results presented in this study clearly support this assumption. The combined data from both the left anterior descending and circumflex coronary artery ligations show that R-wave amplitude increases are sensitive and specific predictors of malignant ventricular arrhythmias during the first 10 minutes of acute canine myocardial ischemia. Typically, R-wave amplitude changes preceded the occurrence of arrhythmias by a mean of approximately 1 minute 30 seconds.

The circumflex coronary artery is the dominant coronary vessel in the dog. Its proximal ligation involves a large mass of myocardium, which presumably accounts in part for the high incidence of malignant ventricular arrhythmias. Intramyocardial conduction delay and fragmentation after circumflex ligation involves a large area of myocardium which may, in turn, account for the appearance of significant R-wave amplitude changes on the surface electrocardiogram. In contrast, ligation of the mid left anterior descending coronary artery involves a smaller mass of myocardial tissue in the dog and is therefore associated with a lower incidence of malignant ventricular arrhythmias. Because intramyocardial conduction abnormalities are confined to a relatively smaller region of myocardium, they are not as readily reflected as R-wave amplitude alterations on the scalar electrocardiogram. The fact that the results of both the circumflex and left anterior descending coronary artery ligations were analyzed in each dog

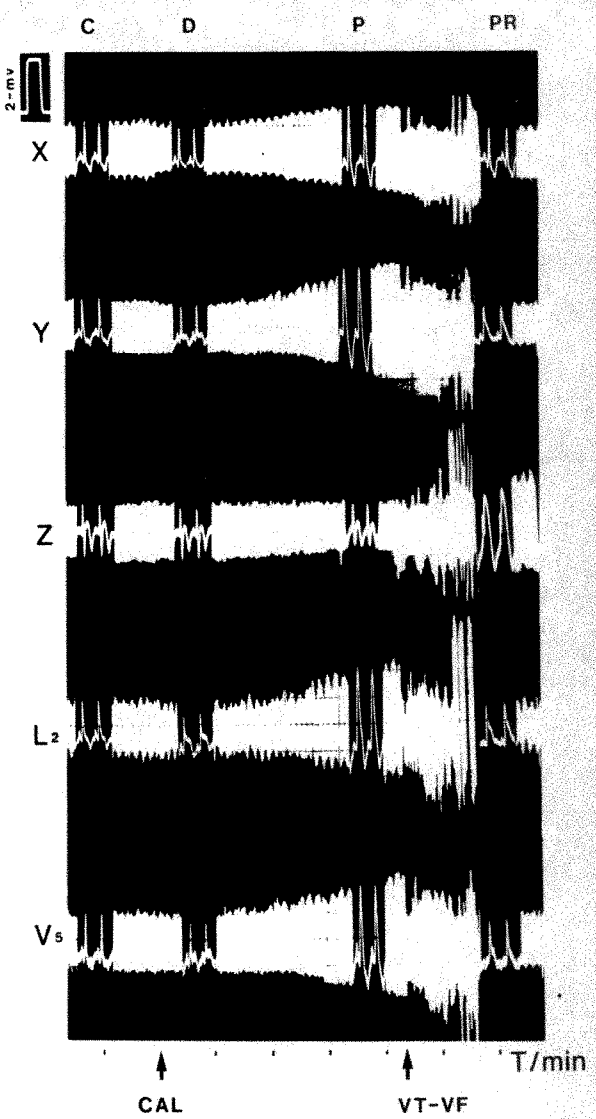

FIGURE 2. Electrocardiographic trend recording during ligation (CAL) and after reperfusion (PR) of the left circumflex coronary artery in the same dog shown in Figure 1. Frank orthogonal leads X, Y, and Z as well as scalar leads L_2 and V_5 are demonstrated. Representative QRS complexes are shown during the control period (C), 30 seconds after ligation (D), 4 minutes after ligation (P), and immediately after reperfusion and resuscitation from ventricular tachycardia (VT) followed closely by ventricular fibrillation (VF). Note that in each of the leads except Z, the R-wave amplitude shows an initial decrease at time D and subsequently a marked increase, evident at time P, immediately before the initiation of VT/VF. After reperfusion and resuscitation, R-wave amplitudes normalize, but marked S-T and T wave changes can still be detected. An increase in R-wave amplitude of 25% or greater from control is already evident more than 1 minute before the occurrence of VT-VF.

lends further support to these assumptions. These analyses are particularly relevant because differences exist in coronary artery distribution patterns between the dog and man, as already noted. Overall, R-wave amplitude changes were sensitive, specific, and predictive for the occurrence of arrhythmias when both the circumflex and left anterior descending coronary artery

ligations were considered together in our model (Table II).

Clinical implications: There is considerable interest in using noninvasive methods to identify patients at high risk for sudden cardiac death, particularly those susceptible to malignant ventricular arrhythmias. The present study suggests that increases in R-wave amplitude in association with acute ischemia may be a clinically useful marker of susceptibility to malignant arrhythmias. A recent case report[24] lends further clinical support to this hypothesis. This marker may be of major interest in patients who demonstrate marked R wave amplitude increases during exercise testing or ambulatory electrocardiographic monitoring, particularly those with critical coronary artery obstructive disease. Potentially, R-wave changes may provide a useful noninvasive means to select those patients in danger of sudden electrical death, who might then be candidates for further diagnostic and therapeutic procedures. Moreover, R-wave amplitude increases may herald the onset of malignant ventricular arrhythmias in patients with recurrent severe ischemic episodes hospitalized in the coronary care unit.

To further facilitate the potential application of our findings to the human situation, we have reported the results of R-wave amplitude increases both in 5 monitored surface electrocardiographic leads (X, Y, Z, L_2, and V_5) as well as in leads L_2 and V_5, the leads most commonly used during exercise testing. Importantly, our results indicate that R-wave amplitude increases using leads L_2 and V_5 are comparable in their predictive value to the sum of R wave amplitude increases using more elaborate monitoring systems (Table I).

In summary, in this canine model of acute myocardial ischemia, R-wave amplitude increases were highly sensitive, specific, and predictive of malignant ventricular arrhythmias. Both R-wave amplitude changes and malignant arrhythmias may be related to the marked delay in intramyocardial conduction that occurs acutely in the ischemic zone. Clinical investigation of this phenomenon should be of considerable interest in the identification of patients at increased risk for sudden death.

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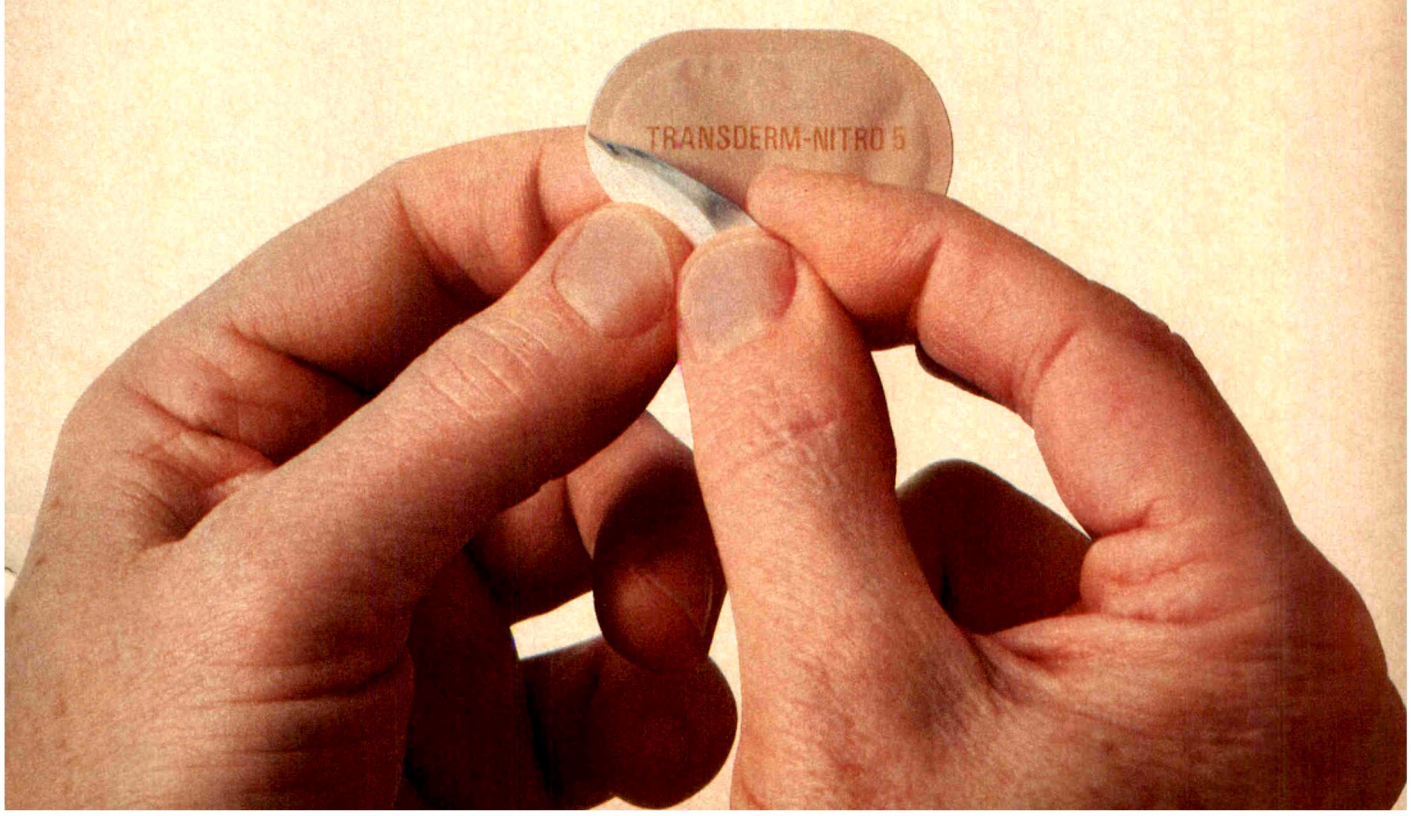

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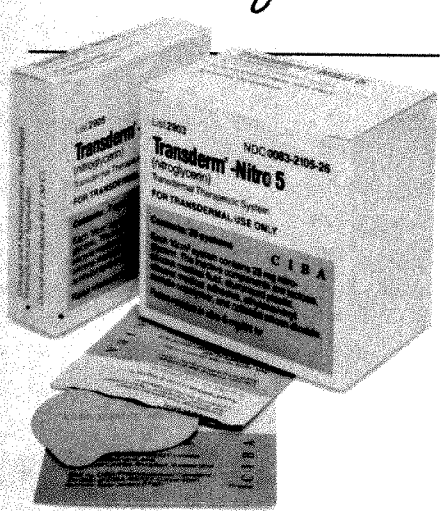

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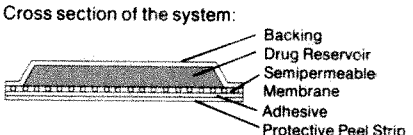
Cross section of the system:



ACTIONS
When the Transderm-Nitro system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In clinical studies transdermal absorption of nitroglycerin from a nitroglycerin system occurred in a continuous and well-controlled manner, for a minimum of 24 hours. Therapeutic effect can be anticipated 30 minutes after application of the system and to be maintained for 30 minutes after its removal.

INDICATIONS AND USAGE
Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring. In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.
Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist, the dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response.

The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.

Do not store above 86°F (30°C).

PATIENT INSTRUCTIONS FOR APPLICATIONS
A patient leaflet is supplied with the systems.

HOW SUPPLIED

Transderm-Nitro System Rated Release *in vivo*	Total Nitroglycerin in System	System Size	Carton Size
5 mg/24 hr	25 mg	10 cm^2	30 Systems (NDC 0083-2105-26)
5 mg/24 hr	25 mg	10 cm^2	7 Systems (NDC 0083-2105-07)
10 mg/24 hr	50 mg	20 cm^2	30 Systems (NDC 0083-2110-26)

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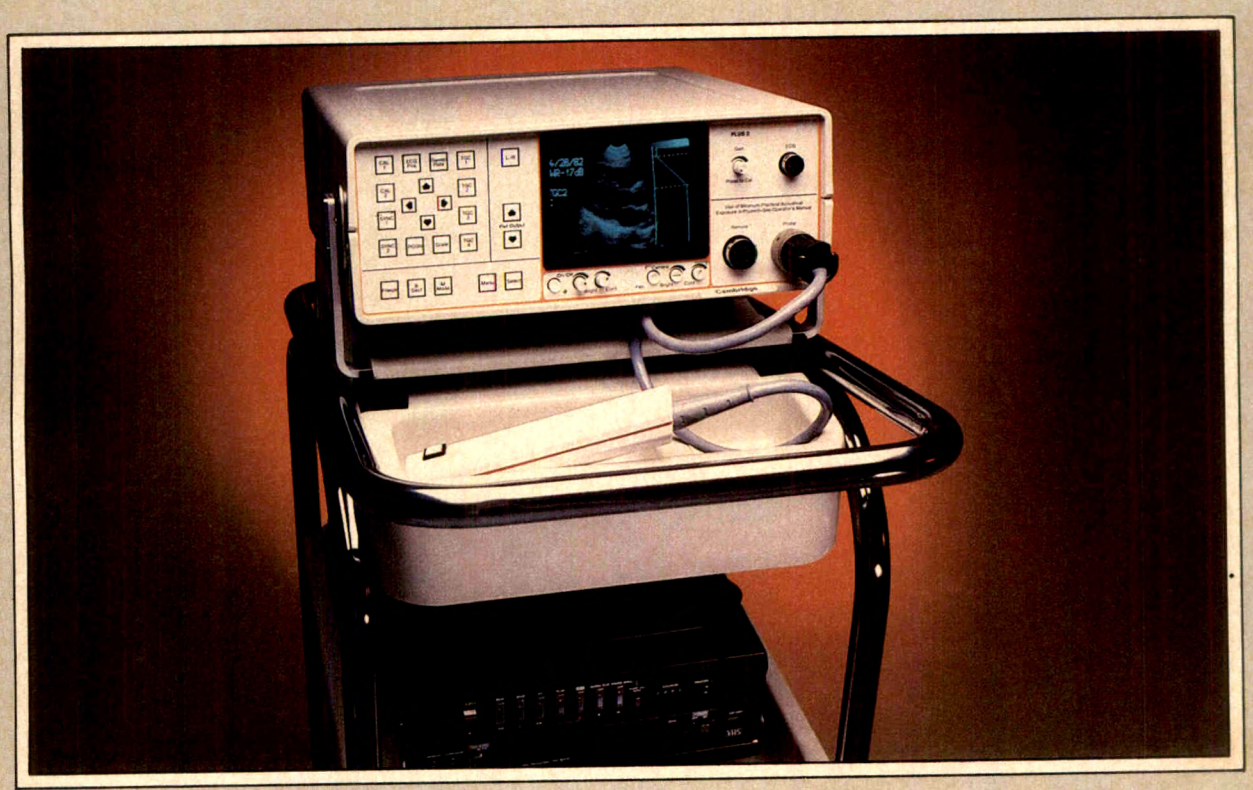

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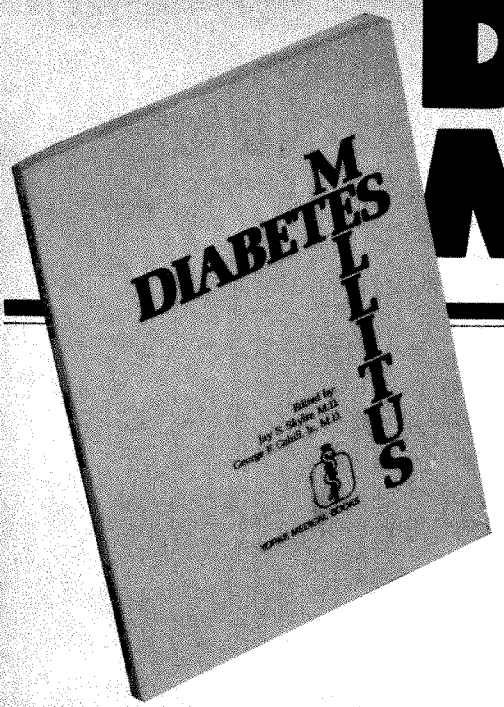

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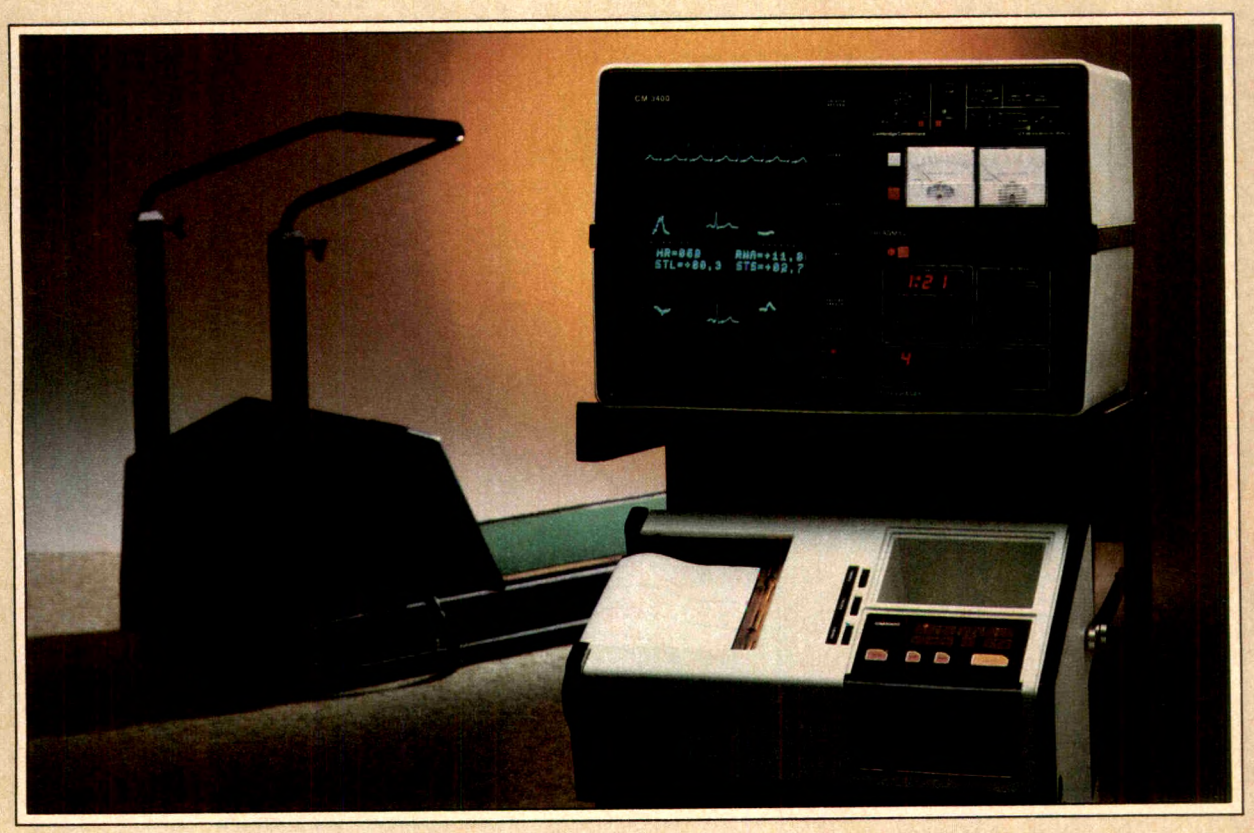

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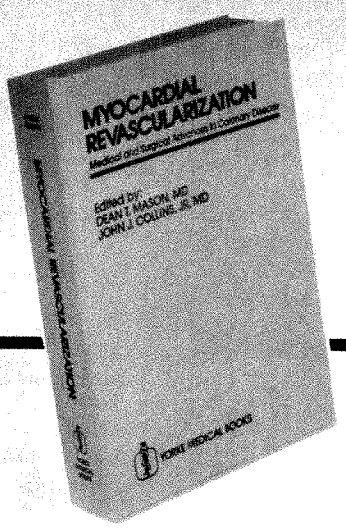

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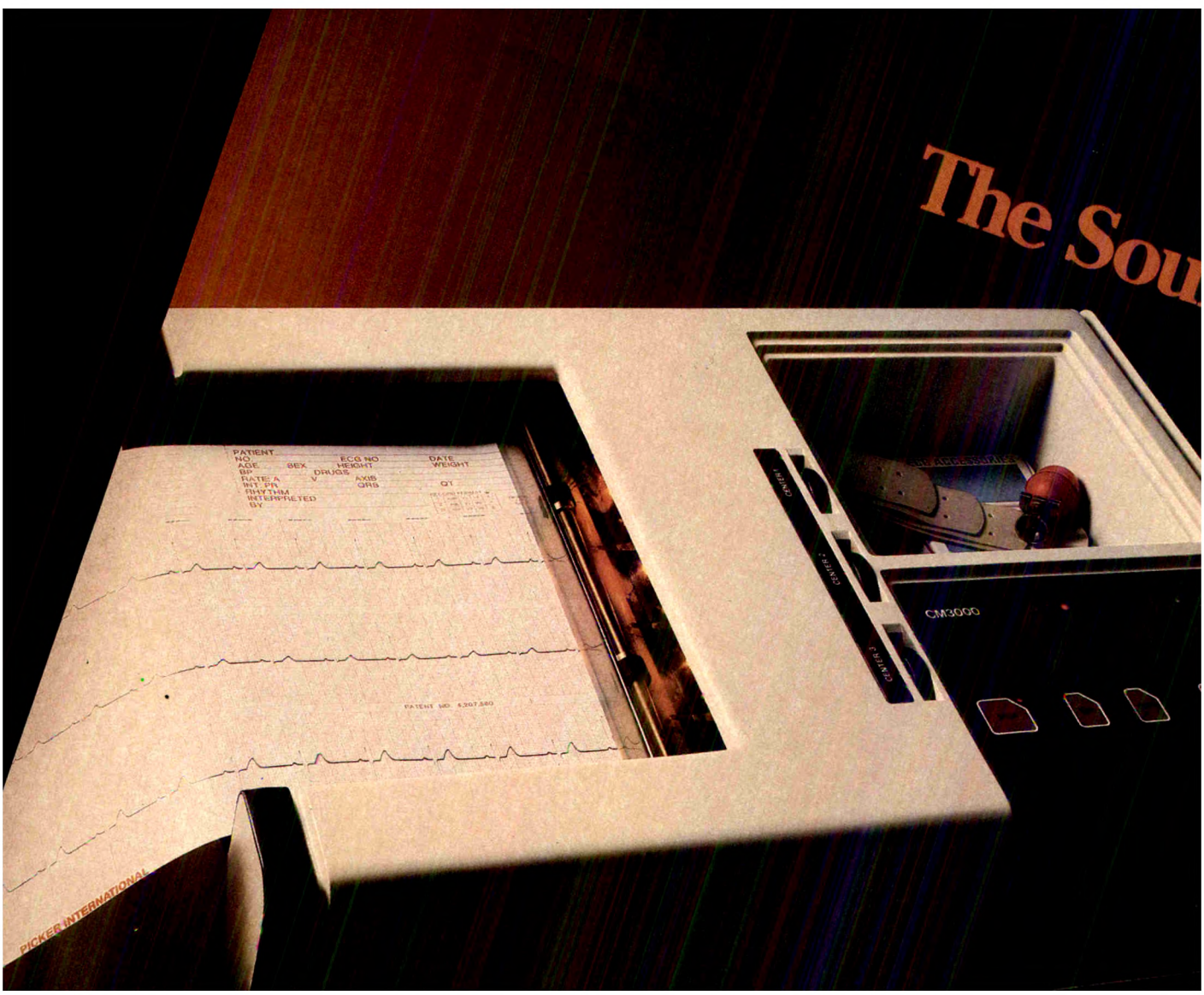
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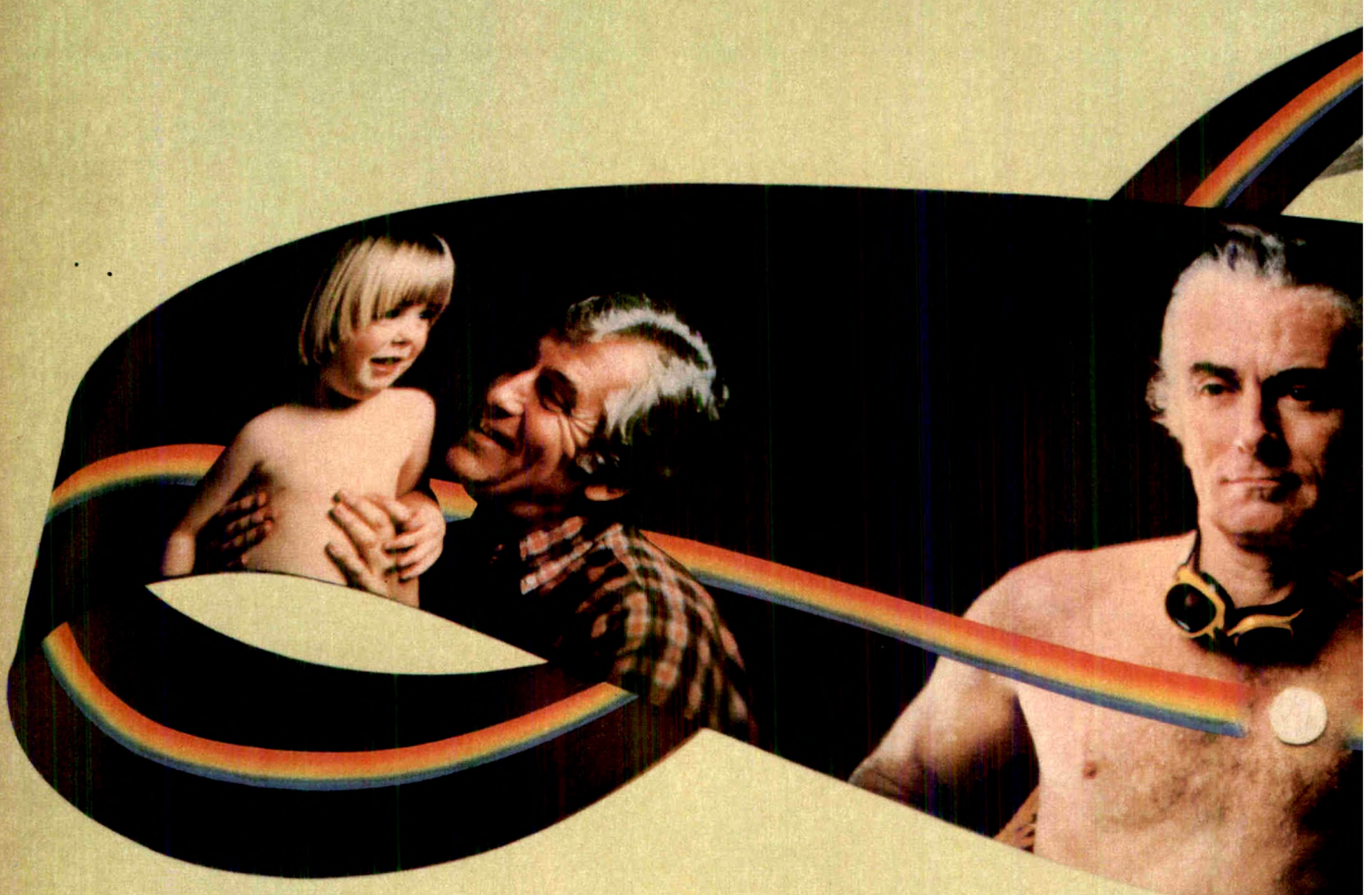
NITRODISC™

(nitroglycerin) 5-MG/24-HR; 10-MG/24-HR PAD

Continuous anginal



Contraindications for nitroglycerin include patients with increased intraocular pressure. Side effects include headache, hypotension, flushing, and dizziness. In terminating treatment, both the dosage and frequency of application must be gradually reduced during a period of four to six weeks.

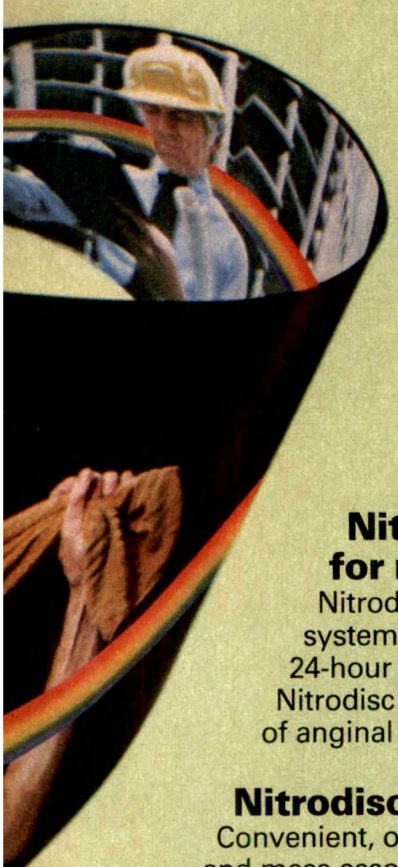
protection...q.d.

Preliminary results from a clinical study indicate 24-hour improvement in exercise capacity

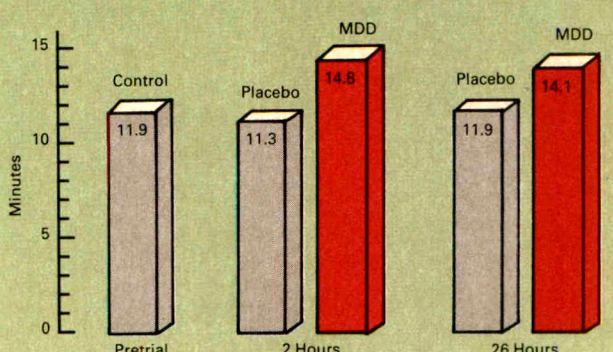
Until now, the clinically recognized benefits of a single nitrate dose have not been documented beyond 12 hours.

In a controlled study,[1] Searle's new nitroglycerin Microseal Drug Delivery™ (MDD) system provided an 18% average increase in exercise capacity 26 hours after application.[2]

In addition, the need for sublingual nitroglycerin was reduced.



Mean Exercise Duration



Nitrodisc (nitroglycerin) eliminates the need for multiple doses of long-acting oral nitrates

Nitrodisc's unique solid polymer releases nitroglycerin into the systemic circulation at a controlled and sustained rate over a 24-hour period.

Nitrodisc (nitroglycerin) is not intended for the immediate relief of anginal attacks.

Nitrodisc enhances compliance

Convenient, once-daily dosage schedule, plus the absence of bother and mess associated with nitroglycerin ointments.

Secure, waterproof adhesive allows for a complete range of daily activities.

1 The interim results presented include data on eight patients completing the protocol to date. A total of twenty patients will be included.

2 Thompson RH: Clinical use of transdermal delivery devices with nitroglycerin. Presented at the Medical Therapy for Angina in the 1980s: New Horizons Symposium, Atlanta, April 24, 1982.

In another clinical study conducted among cardiac rehabilitation participants, concomitant Nitrodisc (nitroglycerin) propranolol therapy did not demonstrate a significant improvement over propranolol alone.

Please see the following page for the complete prescribing information.

SEARLE

5-MG/24-HR; 10-MG/24-HR

NITRODISC™

(nitroglycerin)

DESCRIPTION: The Nitrodisc pad incorporates a patented Microseal Drug Delivery™ system consisting of a solid, nitroglycerin-impregnated polymer bonded to a flexible, non-sensitizing adhesive bandage. It is designed to be applied topically. Nitrodisc provides constant and controlled drug delivery over a uniform skin surface area for 24 hours.

Nitrodisc is available in two strengths that release either 5 mg or 10 mg of nitroglycerin during a 24-hour period. The 5 mg/24 hr system contains 16 mg nitroglycerin over an 8 cm^2 releasing surface. The 10 mg/24 hr system contains 32 mg nitroglycerin over a 16 cm^2 releasing surface (see HOW SUPPLIED section).

ACTIONS: When a Nitrodisc pad is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart and peripheral vasculature) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is due to a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In addition, a direct effect of nitroglycerin on the coronary vessels is recognized as well.

In clinical studies, transdermal absorption of nitroglycerin from Nitrodisc occurred in a continuous and well-controlled manner for a minimum of 24 hours. Therapeutic plasma levels were attained within 1 hour after the application of the pad and remained in the therapeutic range for 24 hours. Plasma levels of nitroglycerin were still detectable 30 minutes after removal of the system.

The amount of nitroglycerin released (5 mg/24 hr or 10 mg/24 hr) represents the mean absorption rates through skin determined during clinical evaluations. Absorption may vary among individuals.

INDICATIONS AND USAGE: Nitrodisc is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Nitrodisc (nitroglycerin) is contraindicated in patients known to be intolerant of organic nitrate drugs, and in patients with marked anemia, increased intraocular pressure, or increased intracranial pressure.

WARNINGS: In patients with acute myocardial infarction or congestive heart failure, Nitrodisc should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of patients with angina, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent potential withdrawal reactions, which are characteristic of all vasodilators in the nitrate class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness, or dizziness, particularly orthostatic hypotension, may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Nitrodisc is not intended for immediate relief of anginal attacks. For this purpose, occasional use of sublingual preparations may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Nitrodisc therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist, Nitrodisc (nitroglycerin) dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION: A Nitrodisc pad should be applied once each day. To use the pad, follow the instructions on the package. Nitrodisc should be applied to a skin site free of hair and not subject to excessive movement. It should not be applied to the distal parts of the extremities. A suitable area should be shaved free of hair, if necessary. The application site should be changed slightly each time to avoid undue skin irritation. A new pad should be applied if the product loosens.

The optimal dosage regimen should be selected based upon the clinical response, the side effects, and the effects of therapy upon blood pressure and heart rate. It is recommended that therapy be initiated with the smaller pad, and that the larger pad be utilized when a greater response is desired. In the event that higher doses are necessary, multiple pads may be applied.

PATIENT INSTRUCTIONS FOR APPLICATION: These are provided with the product.

HOW SUPPLIED:

Nitrodisc	5 mg/24 hr	10 mg/24 hr
Drug released per 24 hours	5 mg	10 mg
Total drug content	16 mg	32 mg
Drug releasing surface	8 cm^2	16 cm^2

Nitrodisc pads are supplied in cartons of 30. Store at a controlled room temperature of 59°-86°F (15°-30°C). **Do not refrigerate.** Extremes of temperature and humidity should be avoided.

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Edited by Michael H. Grieco, M.D.
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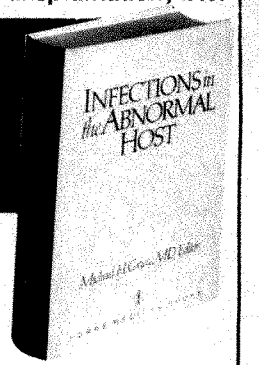

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Ibuprofen-Mediated Infarct Size Reduction: Effects on Regional Myocardial Function in Canine Myocardial Infarction

PHILIP C. KIRLIN, MD,* JOSEPH L. ROMSON, PhD,† BERTRAM PITT, MD, GERALD D. ABRAMS, MD, M. ANTHONY SCHORK, PhD, and BENEDICT R. LUCCHESI, PhD, MD

Normal, marginal, and central ischemic regional myocardial function were evaluated in a canine model of myocardial infarction during 90 minute left circumflex coronary artery occlusion in 25 anesthetized dogs randomly assigned to intravenous ibuprofen infusion (n = 13, 5.36 mg/kg/h beginning 1 hour before occlusion) or vehicle solution as control (n = 12) and in 15 conscious, unsedated dogs 48 and 72 hours after 90 minute circumflex artery occlusion followed by reperfusion (ibuprofen, 5.36 mg/kg/h by intravenous infusion over 7 hours beginning 1 hour before occlusion, n = 7; or vehicle solution infusion as control, n = 8).

Miniature subendocardial sonomicrometer crystal pairs were used to calculate left ventricular regional end-diastolic segment length, end-systolic segment length, and regional percent systolic shortening. Infarct size was estimated in 72 hour animals by a postmortem dual perfusion technique using triphenyltetrazolium histochemical dye and Evan's blue dye for determination of infarct area, risk area, and area not at risk. Ibuprofen treatment significantly reduced infarct size expressed as percent of risk area (mean ± standard deviation of 44.6 ± 18 versus 64.4 ± 16% for control dogs, $p < 0.05$) but it did not improve normal, marginal, or ischemic region end-diastolic length, end-systolic length or percent systolic shortening during coronary occlusion in anesthetized dogs or after reperfusion in conscious animals at 48 and 72 hours, and it did not enhance inotropic reserve at 72 hours in conscious animals. During 90 minute circumflex occlusion in anesthetized dogs, ibuprofen was associated with increases in systemic arterial pressure and worsened ischemic regional percent systolic shortening.

Thus, ibuprofen does not improve normal, marginal, or ischemic zone regional myocardial function during acute ischemia or 48 or 72 hours after myocardial reperfusion despite a significant reduction of infarct size.

Reducing the extent of ischemic injury has been proposed as a rational goal in the management of acute myocardial infarction.[1] Initial attempts to achieve this goal centered primarily on hemodynamic interventions which lessened myocardial oxygen consumption or improved blood flow or oxygen delivery to ischemic myocardium; more recent investigations have evaluated a variety of agents whose primary effect is not hemodynamic but rather anti-inflammatory. The hypothesis supporting the use of these agents is that a significant determinant of ultimate ischemic injury is the inflammatory process itself. Among the many agents currently under evaluation is ibuprofen, a nonsteroidal antiinflammatory agent clinically employed for rheumatic disease.[2] Experimental studies have demonstrated a myocardial protective effect of ibuprofen in a variety of animal models,[3–7] presumably attributable to its antiinflammatory actions which affect arachidonic acid metabolism and consequent physiologic events.[8]

However, few studies on myocardial infarct size reduction involving either hemodynamic or antiinflammatory interventions have addressed the issue of the functional integrity of the salvaged myocardium or the effect of these agents on the function of myocardium removed from the area of ischemic injury. In order to assess the myocardial protective effect of ibuprofen on regional myocardial function, the following investigation was undertaken using implantable subendocardial

From the Departments of Pharmacology, Internal Medicine (Cardiology Division), and Pathology, University of Michigan Medical School and the Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan. This study was supported in part by National Institutes of Health Research Grant HL19782-03 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland, and by a grant-in-aid from the Upjohn Company, Kalamazoo, Michigan. Manuscript received November 30, 1981; revised manuscript received April 27, 1982, accepted May 6, 1982.

* Dr. Kirlin was the recipient of a Michigan Heart Association Research Fellowship Award, Lathrop Village, Michigan.

† Dr. Romson was the recipient of a Pharmaceutical Manufacturer's Association Fellowship, Washington, D.C.

Address for reprints: Benedict R. Lucchesi, MD, Department of Pharmacology, M6322 Medical Science Building I, University of Michigan Medical School, Ann Arbor, Michigan 48109.

sonomicrometer crystals to measure segment length changes in normal, marginal and ischemic regions[9] in a canine model of left circumflex coronary artery occlusion and reperfusion. In this study, regional myocardial function was evaluated in open-chest, anesthetized dogs during coronary artery occlusion and in conscious, unsedated dogs 48 and 72 hours after circumflex occlusion and subsequent myocardial reperfusion.

Methods

Regional Myocardial Function During Coronary Artery Occlusion

Coronary occlusion: In order to assess the acute effects of ibuprofen on regional function during evolving myocardial injury due to coronary artery occlusion, 25 dogs were studied in the open-chest anesthetized state. Healthy male mongrel dogs weighing 10.2 to 18.9 kg (mean ± standard deviation 13.9 ± 1.9) were anesthetized with 30 mg/kg intravenous sodium pentobarbital and mechanically ventilated on room air by a Harvard animal respirator (Harvard Apparatus, Millis, Massachusetts) using an endotracheal tube. A left 5th intercostal space thorocotomy was performed and the pericardium incised and sutured to form a pericardial cradle. The left circumflex coronary artery was isolated distal to the left atrial appendage proximal to major branches. A zone of cyanosis was determined to be at least 9 cm^2 during transient (10 to 15 second) coronary occlusion. Three pairs of commercially manufactured miniature (3 mm) piezoelectric crystals (800 kHz frequency in radial mode with a resolution capability of 0.1 to 0.5 mm) connected to an oscilloscope sonomicrometer (Norland Instruments sonomicrometer crystals and NI-202 sonomicrometer) were implanted 1 to 2 cm apart in the left ventricular subendocardium (Fig. 1). One crystal pair (central ischemic zone) was implanted in the posterolateral left ventricular surface in the center of the cyanotic zone as determined by the transient circumflex occlusion, and a 2nd pair (marginal area) was implanted in the anterolateral left ventricular wall to straddle the border between cyanotic and noncyanotic zones. The marginal area was defined in the present study as a region of intermediate function between normal and ischemic zones.[9] Normal zone sonomicrometer crystals were implanted on the anterior left ventricular wall in the region supplied by the left anterior descending coronary artery well removed from the ischemic area as determined by the zone of cyanosis. The crystals were implanted in a plane perpendicular to the base-apex cardiac axis and secured by an epicardial suture around the connecting wires as they emerged from the myocardium. Repeated calibrations at 1 μs intervals were obtained to eliminate variation due to signal drift.

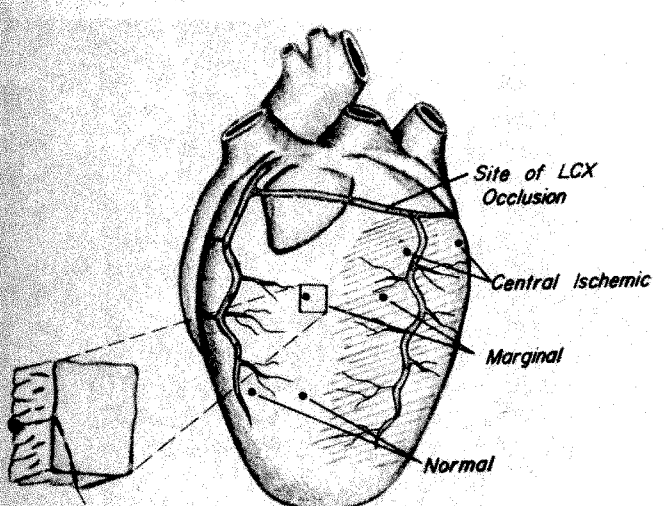

FIGURE 1. Diagram of subendocardial sonomicrometer crystal placement in normal, marginal, and central ischemic left ventricular regions. LCX = left circumflex coronary artery. See text for discussion.

In addition, a small left neck incision was made for insertion of a polyethylene carotid artery catheter for blood pressure measurement and an external jugular catheter for infusion of ibuprofen or control solution. The carotid artery catheter was connected to a Statham P23DC pressure transducer. Mean arterial pressure was calculated as diastolic pressure plus one third of the pulse pressure.

Ibuprofen infusion: Crystalline ibuprofen (sodium salt) was dissolved in 0.2 *M* sodium carbonate and adjusted to a pH of 8 by 1.0 N HCl. Solutions were mixed fresh before each experiment and diluted to 50 ml in physiologic saline solution. The ibuprofen dose employed was 5.36 mg/kg/h (7.14 ml/h of ibuprofen solution) by continuous intravenous infusion beginning 1 hour before occlusion and continuing throughout occlusion (90 minutes). This dose is similar to that used in a previous investigation[6] with the exception of initiation of the infusion before occlusion in the present study. Vehicle solution prepared in an identical manner without ibuprofen served as a control. A Harvard infusion pump was used to provide a constant infusion rate. Animals were randomly assigned to their treatment groups (13 ibuprofen, 12 control). A lead II electrocardiogram was monitored throughout the experiment.

After instrumentation, visible epicardial arterial anastomoses between the left anterior descending and circumflex coronary arteries were ligated to eliminate potentially large collateral routes of blood flow.[10] A subtotal left circumflex coronary artery stenosis was produced just distal to the left atrial appendage by tying 1-0 silk suture around both the artery and an 18 gauge needle followed by immediate needle removal; subsequent total circumflex artery occlusion was performed after 10 minutes with a total duration of occlusion of 90 minutes. Three mg/kg of intravenous lidocaine and 3 mg/kg of intramuscular lidocaine were administered at the time of coronary artery occlusion as antiarrhythmic therapy.[11] Approximately one fourth of the animals developed ventricular fibrillation during coronary occlusion, which was readily converted to sinus rhythm within 30 to 60 seconds by low energy (10 to 20 J) direct current cardioversion using epicardial paddles. No myocardial dysfunction has been reported at these energy levels.[12]

Regional myocardial segment length: Measurement of regional myocardial segment length was obtained by converting sonomicrometer crystal transit time in microseconds to distance in millimeters using a known value for the velocity of ultrasound in myocardium at the frequency employed: Distance (mm) = transit time (μs) × ultrasound velocity in myocardium (1.58 mm/μs).[13] Before occlusion, end-diastolic length was defined in each segment as the maximal crystal separation in millimeters before the onset of the carotid artery systolic pressure rise, and end-systolic length was defined as the minimal crystal separation in millimeters before the dicrotic notch of the carotid artery pressure tracing. Nonsimultaneous end-diastolic or end-systolic timing in marginal or

ischemic segments in relation to normal segments was noted before occlusion and used as a reference to determine end-diastole and end-systole in the presence of dyskinesia during coronary artery occlusion. Measurement of absolute end-diastolic and end-systolic length in millimeters were obtained and regional percent systolic shortening defined as end-diastolic minus end-systolic length divided by end-diastolic length ×100%. Subendocardial crystal placement was confirmed by postmortem examination.

A Grass model 7 polygraph was used to record measurements at a paper speed of 100 mm/s. Determination of carotid artery pressure, heart rate, and regional segment lengths and percent systolic shortening were obtained before and at the end of 90 minutes of coronary occlusion. All measurements were obtained at end-expiration and when the animal was free of arrhythmias.

Regional Myocardial Function 48 and 72 Hours After Coronary Artery Occlusion-Reperfusion

The effect of ibuprofen on regional myocardial function and infarct size was evaluated in conscious, unsedated dogs after left circumflex coronary artery occlusion with subsequent myocardial reperfusion in the anesthetized state. Fifteen healthy male mongrel dogs weighing 13.6 ± 1.5 kg (range 10.2 to 15.8) were used. Instrumentation, baseline regional function measurements, and 90 minute circumflex occlusion followed by reperfusion were performed using aseptic technique in pentobarbital anesthetized, open-chest dogs as in the acute occlusion study. Animals were randomly assigned to either ibuprofen (n = 7) or vehicle as control (n = 8). Solutions were prepared as before and administered intravenously by Harvard infusion pump over 7 hours beginning 1 hour before occlusion with an ibuprofen dose of 5.36 mg/kg/h (7.14 ml/h of ibuprofen solution) or with an identical volume of vehicle as a control. Ischemic zone sonomicrometer crystals were associated with greater postoperative mortality in preliminary studies and therefore implanted in only 4 animals in each group. As in the acute occlusion study, a critical circumflex stenosis was placed 10 minutes before total occlusion using an 18 gauge needle and 1-0 silk suture. A Carolina Medical Electronics electromagnetic flow probe was placed around the circumflex artery proximal to the subtotal occlusion to document a critical stenosis (defined as a stenosis causing at least a 50% reduction in peak reactive hyperemic flow after 10 seconds of coronary occlusion without altering basal flow or sonomicrometer crystal segment length). This subtotal critical stenosis was left in place throughout the remainder of the experiment (until the animals were killed at 72 hours).

Coronary occlusion and reperfusion: Total left circumflex occlusion was performed using soft plastic tape for 90 minutes and the occlusion was slowly released over 5 to 10 minutes. Intravenous lidocaine, 3 mg/kg, was administered on reperfusion. Reperfusion occurred in all animals as documented by 3 or more of the following criteria: (1) the onset of ventricular arrhythmias within 15 to 30 minutes of occlusion release; (2) a decrease in marginal and ischemic region end-diastolic and end-systolic segment length on release of the occlusion; (3) at least 5 ml/min of circumflex artery flow on occlusion release documented by electromagnetic flow probe; and (4) the absence of visible coronary artery thrombosis at 72 hours when the animal was killed.

After reperfusion, the chest was closed and the animals were allowed to recover. Intramuscular ampicillin, 6 mg/kg, was administered twice on the day of surgery and daily thereafter. No recordings were obtained until 48 hours after surgery because of frequent ventricular arrhythmias. At 48 and 72 hours, recordings of sonomicrometer crystal segment lengths were obtained in the conscious, unsedated state with the animal standing upright in a nylon sling. In order to assess residual ventricular contractile function, inotropic reserve was also tested at 72 hours after coronary occlusion-reperfusion, 5 minutes after administration of the beta-adrenergic stimulant prenalterol (30 μg/kg intravenous bolus).[14]

Determination of infarct size and risk area: Animals were then reanesthetized with sodium pentobarbital, the chest was reopened, and the hearts were electrically fibrillated and rapidly excised for immediate postmortem in vitro determinations of infarct size and risk area by a dual perfusion technique using 4% triphenyltetrazolium chloride mixed with phosphate buffer for histochemical staining of dehydrogenase enzyme and 0.5% Evan's blue flow-dependent staining as described in detail elsewhere.[7,15] Briefly, this method involves simultaneous selective left circumflex perfusion with triphenyltetrazolium and nonselective retrograde aortic perfusion with Evan's blue dye at physiologic pressure (100 mg Hg), with the resultant Evan's blue staining tissue identifying the area not at risk of ischemic injury and the remaining tissue representing the area at risk with red triphenyltetrazolium staining tissue identifying the viable, noninfarcted region, and the remaining tissue (unstained) representing the area of infarction. After staining, the heart was sliced from apex to base in 5 mm thick transverse sections and the atria and right ventricle were excised. Left ventricular weight was recorded and left ventricular slices were traced on transparent plastic sheets for hand planimeter determination of left ventricular area, area at risk, and area of infarction. Infarct size was measured as percent of area at risk and percent of total left ventricular area. The anatomic perfusion bed of an occluded coronary has been shown to correlate well with the area at risk of infarction in experimental canine coronary artery occlusion.[10] Subendocardial crystal placement was also confirmed at postmortem evaluation.

Light microscopic evaluation of hematoxylin and eosin stained left ventricular slices was performed in a blinded manner on 72 hour specimens from all animals in each group to assess the morphologic integrity of myocardial cells and the inflammatory response.

Statistical methods: All results are expressed as mean ± 1 standard deviation. Statistical analysis was performed by a computerized statistical program of the University of Michigan Statistical Research Laboratory (Michigan Interactive Data Analysis System). Two factor analysis of variance for repeated measures (profile analysis)[16] was employed for the same variable measured more than twice, and paired or unpaired *t* test was performed as appropriate on data measured only twice. A probability value (p) less than 0.05 was considered significant.

Results

Regional myocardial function during coronary artery occlusion: In anesthetized, open-chest dogs 90 minute circumflex coronary artery occlusion resulted in a marked alteration of contractile function manifested by greatly diminished marginal and ischemic segment systolic shortening and increased end-diastolic and end-systolic segment lengths in all 3 regions, indicative of ischemia-associated ventricular dilation[9] (Fig. 2, Table I). Ibuprofen administration did not decrease these segment length increases or improve systolic shortening in any region during coronary artery occlusion. In the central ischemic zone, ibuprofen-treated animals developed more severe impairment of

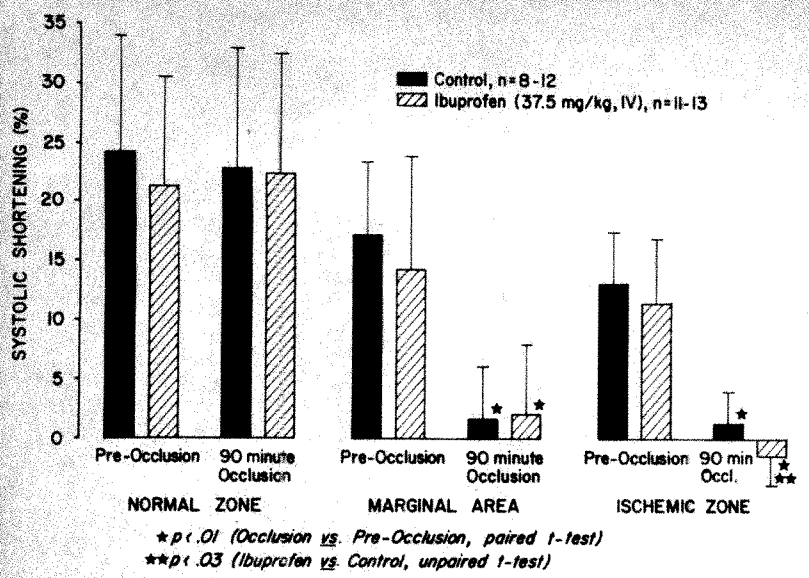

FIGURE 2. Effect of ibuprofen on regional myocardial function after 90 minute left circumflex coronary artery occlusion. Marginal and ischemic zone percent systolic shortening was reduced in both groups compared with preocclusion (paired *t* test), and ibuprofen animals had significantly worse systolic shortening than controls in the ischemic zone at the end of the 90 minute occlusion (unpaired *t* test).

systolic shortening with paradoxic systolic expansion (dyskinesia). Heart rate was not altered by ibuprofen during coronary occlusion; however, mean carotid artery pressure rose significantly with a rise in pressure-rate product (the product of mean arterial pressure and heart rate divided by 100) (Table I).

Regional myocardial function 48 and 72 hours after coronary artery occlusion-reperfusion: Serial changes in regional myocardial function in a control animal before, during, and up to 72 hours after coronary artery occlusion-reperfusion are shown in Figure 3. Similar baseline regional myocardial function was present in ibuprofen-treated and control animals in the anesthetized, open-chest state before coronary occlusion (Table II, Fig. 4 to 6). In the conscious, unsedated state 48 and 72 hours after occlusion with myocardial reperfusion, both marginal and ischemic zone systolic shortening were impaired despite partial recovery, while normal zone systolic function remained relatively unaltered. Ibuprofen treatment did not improve systolic function or decrease ventricular end-diastolic or end-systolic segment lengths in normal, marginal, or ischemic regions at 48 hours or 72 hours before or after inotropic stimulation.

A significant reduction in the extent of ischemic injury as measured by percent of the area at risk infarcted was noted in ibuprofen-treated animals (44.6 ± 18%) compared with control animals (64.4 ± 16%, p

TABLE I Effects of Ibuprofen During Coronary Occlusion

	Heart Rate (beats/min)		Mean Arterial Pressure (mm Hg)		Pressure-Rate Product		Normal Zone: End-Diastolic Length (mm)		Normal Zone: End-Systolic Length (mm)		Normal Zone: % Systolic Shortening	
	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen
Baseline	167 ±25	159 ±17	111 ±14	120 ±20	187 ±46	194 ±50	12.6 ±3.1	14.7 ±2.4	9.7 ±3.2	11.5 ±2.3	24.3 ±9.7	21.4 ±9.2
90 minute coronary occlusion	171 ±20	174 ±18	106 ±14	137 ±15*	178 ±30	239 ±44*	14.6 ±4.0	17.1 ±3.0	11.4 ±3.9	13.3 ±3.1	23.0 ±9.9	22.5 ±10.0

	Marginal Zone: End-Diastolic Length (mm)		Marginal Zone: End-Systolic Length (mm)		Marginal Zone: % Systolic Shortening		Ischemic Zone: End-Diastolic Length (mm)		Ischemic Zone: End-Systolic Length (mm)		Ischemic Zone: % Systolic Shortening	
	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen
Baseline	15.0 ±2.9	13.9 ±5.2	12.5 ±3.0	12.1 ±5.3	17.2 ±6.3	14.3 ±9.7	15.6 ±4.6	17.1 ±4.6	13.6 ±4.2	15.3 ±4.6	13.3 ±4.2	11.6 ±5.5
90 minute coronary occlusion	18.1 ±2.8	17.2 ±6.0	17.8 ±3.1	16.8 ±5.9	1.7 ±4.4	2.1 ±5.9	18.4 ±5.4	19.7 ±5.2	18.1 ±4.9	20.0 ±5.1	1.3 ±2.7	−1.5 ±2.3†

* $p < 0.003$; † $p < 0.03$ (both unpaired *t* test).
Pressure rate product = mean arterial pressure × heart rate divided by 100. Values are mean ± 1 standard deviation.

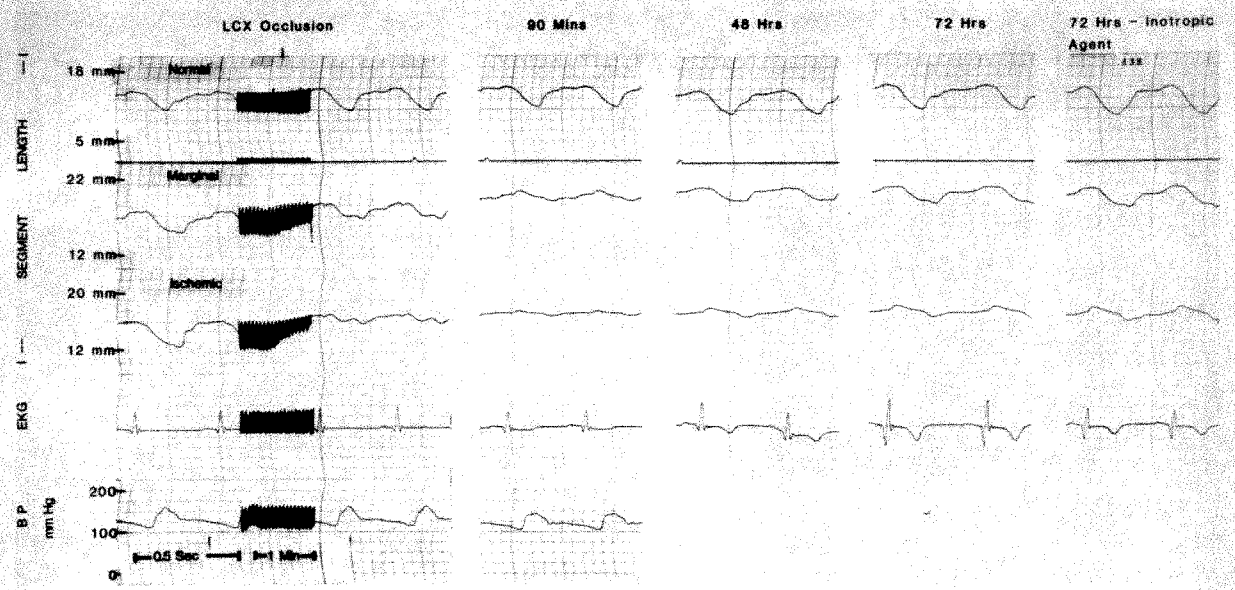

FIGURE 3. Serial changes in normal, marginal, and central ischemic segment length in a control animal before and at the end of 90 minute circumflex occlusion and 48 and 72 hours after reperfusion, and with inotropic stimulation (intravenous prenalterol, 30 μg/kg) at 72 hours. Acute effects of circumflex occlusion on regional myocardial function and evolutionary electrocardiographic changes of infarction are demonstrated. BP = blood pressure; EKG = lead II electrocardiogram; LCX = left circumflex coronary artery.

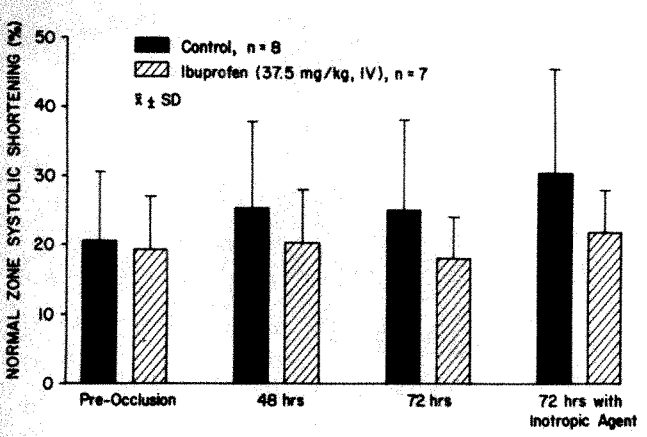

FIGURE 4. Effect of ibuprofen on normal zone regional myocardial function before circumflex occlusion and in conscious, unsedated animals at 48 and 72 hours and with inotropic stimulation at 72 hours. No significant differences were present between groups (analysis of variance for repeated measures). IV = intravenous; SD = standard deviation.

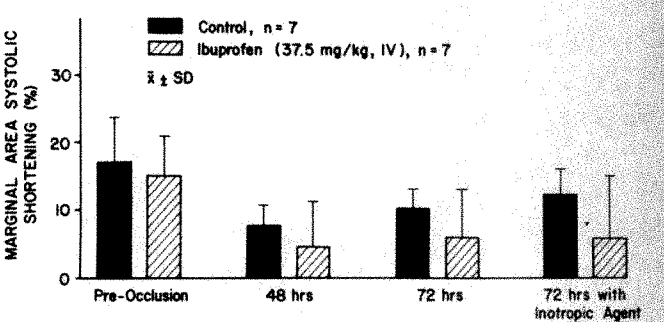

FIGURE 5. Effect of ibuprofen on marginal area regional function (as in Figure 4). No significant differences between groups were present (analysis of variance for repeated measures).

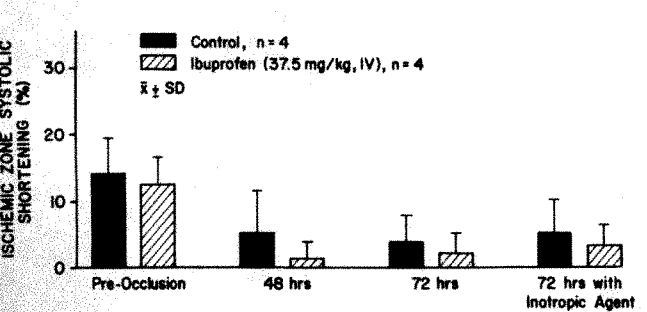

FIGURE 6. Effect of ibuprofen on central ischemic zone regional function (as in Figure 4). No significant differences between groups were present (analysis of variance for repeated measures).

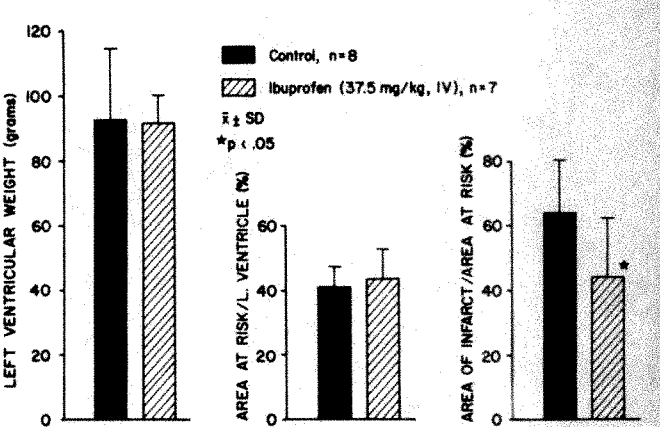

FIGURE 7. Effect of ibuprofen on infarct size. No differences were present between ibuprofen and control animals in left (L.) ventricular weight or area at risk; ibuprofen significantly reduced infarct size expressed as percentage of area at risk (unpaired *t* test).

TABLE II Effects of Ibuprofen on Regional Myocardial Function After Reperfusion

	Normal Zone						Marginal Zone				Ischemic Zone			
	End-Diastolic Length (mm)		End-Systolic Length (mm)		% Systolic Shortening		End-Diastolic Length (mm)		End-Systolic Length (mm)		% Systolic Shortening		End-Diastolic Length (mm)		End-Systolic Length (mm)		% Systolic Shortening	
	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen	Control	Ibuprofen
Baseline	13.3 ±2.6	15.2 ±2.1	10.6 ±2.9	12.2 ±2.4	20.7 ±9.8	19.4 ±7.9	14.9 ±3.1	15.8 ±5.0	12.5 ±3.4	13.5 ±4.8	17.3 ±6.6	15.2 ±5.8	15.5 ±4.1	17.6 ±2.2	13.4 ±4.1	15.4 ±2.6	14.1 ±5.4	12.6 ±4.1
48 hours after reperfusion	15.3 ±2.8	17.0 ±3.5	11.5 ±3.7	13.6 ±3.3	25.5 ±12.7	20.3 ±7.9	17.7 ±3.0	19.1 ±5.2	16.3 ±2.8	18.4 ±5.7	7.8 ±3.0	4.5 ±6.8	17.6 ±3.7	18.5 ±2.4	16.6 ±3.8	18.3 ±2.7	5.3 ±6.4	1.5 ±2.5
72 hours after reperfusion	15.1 ±2.4	16.7 ±3.8	11.4 ±3.4	13.7 ±3.9	25.3 ±13.0	18.3 ±6.0	17.9 ±3.4	19.0 ±5.7	16.1 ±3.1	18.1 ±6.5	10.0 ±3.1	6.0 ±7.1	17.2 ±4.2	18.9 ±3.2	16.5 ±3.9	18.5 ±3.5	4.0 ±4.1	2.3 ±2.8
72 hours with inotropic agent	14.5 ±2.3	15.4 ±3.8	10.2 ±3.4	12.1 ±3.7	30.8 ±1.5	22.3 ±6.1	17.4 ±3.2	18.2 ±5.6	15.3 ±3.1	17.3 ±6.4	12.5 ±3.8	6.2 ±9.0	17.1 ±4.3	18.7 ±3.3	16.2 ±3.9	18.1 ±3.7	5.2 ±5.1	3.5 ±3.0

Values are mean ± 1 standard deviation. Differences between ibuprofen and control groups were not significant (analysis of variance for repeated measures).

<0.05, unpaired t test) despite a similar area at risk and left ventricular weight (Fig. 7). The percent of total left ventricle infarcted was substantially reduced by ibuprofen (19.7 ± 9.1% versus 26.0 ± 5.5% for controls), but this did not reach significance ($p = 0.12$, unpaired t test). By visual inspection of stained ventricular slices, the predominant area of tissue salvage in ibuprofen-treated animals was at the epicardial and lateral margins of the infarct.

Light microscopic analysis of hematoxylin and eosin stained left ventricular slices revealed no evident differences in the extent of inflammatory infiltrate or hemorrhage or in the appearance of necrotic myocardial cells. The appearance of contraction band lesions and of fibroblastic proliferation was comparable in both groups.

Visual inspection of the left circumflex coronary artery after death demonstrated no detectable thrombus in ibuprofen-treated animals and visible thrombus in 1 of 8 control animals.

Discussion

Rationale for this model: Coronary artery occlusion with myocardial reperfusion through a critical stenosis as employed in this model may more closely simulate the evolution of human myocardial infarction than permanent coronary artery occlusion. DeWood et al.[17] demonstrated a progressive decline in the prevalence of total coronary occlusion over 24 hours in patients with acute myocardial infarction, a finding consistent with coronary artery spasm superimposed on fixed obstructive disease[18] or with partial resolution of a coronary artery thrombosis,[17] or both. In addition, experimental animal data indicate that reperfusion may enhance survival[19] and improve the likelihood of myocardial functional recovery.[20] Thus, a rationale exists for the coronary artery occlusion-reperfusion model of myocardial infarction.

Possible mechanisms of ibuprofen's myocardial protective effect: The present study demonstrates a myocardial protective effect of ibuprofen during experimental myocardial infarction without improvement of normal, marginal, or ischemic regional myocardial function during coronary artery occlusion or 48 or 72 hours after reperfusion or of inotropic reserve at 72 hours. The reduction in infarct size noted with ibuprofen in this study is consistent with previous investigations[3–7] employing a variety of dosage schedules and routes of administration. While the mechanisms of infarct size reduction mediated by ibuprofen have not been established, several possibilities have been evaluated.

First, it is unlikely that ibuprofen exerts a hemodynamic effect through diminished myocardial oxygen consumption or increased myocardial blood flow. Jugdutt et al.[6] and Romson et al.[7] noted no significant effect of ibuprofen on blood pressure or heart rate during myocardial ischemia, and the drug has only a minimal effect on ventricular contractile force.[4] In our present study, continuous ibuprofen infusion beginning 1 hour before ischemia resulted in significant elevations of systemic arterial pressure (Table I) without an effect

on heart rate after 90 minutes of coronary occlusion. This result, not found in previous investigations employing different models of ischemia and different drug administration schedules, would increase rather than decrease myocardial oxygen consumption and thus tend to worsen ischemic injury.[21] In addition, directly measured myocardial oxygen consumption is not altered by ibuprofen administration during 60 minutes of normothermic global ischemia in the isolated, blood-perfused feline heart.[15]

Increased blood flow to ischemic tissue by direct coronary artery vasodilation or enhanced collateral blood flow is also an unlikely mechanism of ibuprofen's beneficial effect. Tracer microsphere studies in experimental myocardial infarction have failed to demonstrate increased blood flow to ischemic tissue up to 6 hours[6] or 24 hours[15] after coronary occlusion in ibuprofen-treated experimental animals.

An antithrombotic effect of ibuprofen is a 2nd possible mechanism by which ibuprofen may reduce infarct size.[7] In the present study, however, coronary artery reperfusion occurred in all animals and only 1 of 8 control animals developed visible thrombus at 72 hour postmortem examination. Also, the antithrombotic agent sulfinpyrazone does not appear to reduce infarct size.[22] Thus, it is improbable that an antithrombotic effect of ibuprofen played a role in the present study. The potentially related phenomenon of platelet deposition at the site of ischemic injury also occurs in myocardial infarction and is diminished by aspirin.[23] Ibuprofen, however, does not alter indium-111–labeled platelet accumulation in the ischemic myocardium.[24]

A 3rd possible mechanism by which ibuprofen may exert a myocardial protective effect is its antiinflammatory action, related to inhibition of the arachidonic acid pathway.[8] Cyclooxygenase enzyme inhibition could have a beneficial effect in ischemic tissue through a reduction in the synthesis of thromboxane, a potent vasoconstrictor. However, other nonsteroidal cyclooxygenase inhibitors do not reduce the extent of experimental ischemic injury.[22,25,26] An alternative hypothesis also related to the arachidonic acid cascade which may in part explain ibuprofen's beneficial effect in myocardial ischemia is inhibition of the lipoxygenase pathway. This branch of the arachidonic acid cascade is capable of producing powerful chemotactic substances (hydroxyeicosatetraenoic acid [HETE] derivatives)[27] and leukotrienes, which are additional mediators of the inflammatory response.[27] Ibuprofen has been shown to inhibit the synthesis of 12-HETE, catalyzed by a putative peroxidase enzyme.[28] Lipoxygenase pathway inhibition may in part account for ibuprofen's ability to inhibit the migration of polymorphonuclear leukocytes,[29] an effect noted with ibuprofen in experimental myocardial ischemia.[24]

A 4th mechanism of potential significance in explaining ibuprofen's myocardial protective action is inflammatory cell lysosomal membrane stabilization, an effect suggested by data from noncardiac in vitro preparations[30–32] and by indirect evidence in canine cardiac ischemia.[4] In addition, ibuprofen affects kinin and histamine release[2] and superoxide radical formation,[33,34] which may in part account for its anti-inflammatory effect.

The use of lidocaine in our study could also reduce the severity of myocardial ischemic injury.[35] Our data, however, indicate extensive infarction despite lidocaine administration and an additional beneficial effect of ibuprofen if lidocaine myocardial preservation occurred.

Discordance between infarct size reduction and functional recovery: The discrepancy between myocardial infarct size and functional recovery in this investigation may be due to several factors. Improvement in regional myocardial function may occur at a time not evaluated in this study. A functionally beneficial effect of ibuprofen between the onset of reperfusion and 48 hours cannot be excluded; in the present study a functional assessment was not performed during that time because of marked beat-to-beat segment length changes associated with frequent reperfusion arrhythmias. Alternatively, improvement in myocardial function with ibuprofen could occur at a time later than 72 hours. This possibility is supported by sonomicrometer crystal data in conscious dogs studied up to 4 weeks after 2 hour coronary artery occlusion.[20] Substantial recovery of marginal and ischemic segment systolic shortening occurred 1 to 4 weeks after coronary artery occlusion-reperfusion. Further studies will be necessary to determine whether ibuprofen treatment alters regional myocardial function more than 3 days after myocardial infarction.

Improvement in indexes of myocardial function other than subendocardial segment length changes is another possible explanation of the discordance between infarct size reduction and functional recovery in this investigation. Roan et al.[36] noted spontaneous improvement in ischemic zone ventricular wall paradoxic systolic thinning between 24 hours and 1 week after coronary artery occlusion. Other measures of regional function which were not evaluated in this study include mid-myocardial and subepicardial segment length changes, which may have been altered more than subendocardial functional measurements in view of predominant subepicardial tissue salvage by gross inspection.

A persistent inability of ibuprofen to significantly improve marginal or ischemic region myocardial function despite infarct size reduction as determined by histochemical staining is also possible. Glucocorticoids have been implicated in "mummification" of ischemic myocardium (loss of nuclei with intact myofibril striations and sarcolemma).[37] Such tissue may retain the ability to stain dehydrogenase with triphenyltetrazolium despite the loss of functional integrity. The absence of such a "mummification" effect on light microscopic evaluation in this investigation provides evidence against that possibility.

A recent publication by Kloner et al.[38] demonstrated that a 15 minute period of coronary occlusion followed by reperfusion, which is not associated with the development of necrosis, nonetheless results in prolonged biochemical, functional, and ultrastructural abnormalities. Wall motion, as determined by ultrasonic

crystal measurements, was still reduced at 3 days of reperfusion, whereas creatine phosphate levels and regional myocardial blood flow recovered rapidly and had returned to normal after 90 minutes of coronary reperfusion. Brief periods (15 minutes) of regional ischemia followed by full reperfusion, therefore, can be associated with abnormalities in cardiac contractile function which persist for a relatively long period. Bush et al.[39] showed that the biochemical abnormalities associated with regional ischemia after reperfusion also extend to the normally perfused myocardium. Thus, a regional ischemic event may produce an influence on a remote region of myocardium which may persist for several days after the restoration of coronary blood flow.[38,39]

In the present investigation, coronary artery occlusion was maintained for 90 minutes and was followed by reperfusion in the presence of a critical stenosis. It is conceivable that the failure of the salvaged myocardial segment to regain contractile function could be related to the relatively persistent derangement in segment length shortening which is seen even in the absence of cellular necrosis. Future attempts to assess the potential benefits of pharmacologic interventions in protecting ischemic myocardium should consider the functional recovery of the "salvaged" myocardium days to weeks after the ischemic episode.

Implications: Intravenous ibuprofen infusion reduces myocardial infarct size without improving normal, marginal, or ischemic region myocardial function during coronary artery occlusion or 48 or 72 hours after myocardial reperfusion, or inotropic reserve at 72 hours. Further studies are necessary to assess ibuprofen's effect on regional myocardial function at intervals greater than 72 hours after myocardial infarction and to further elucidate the mechanisms by which ibuprofen exerts a protective effect on ischemic myocardial tissue.

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Protective Effects on Isolated Hearts With Developing Infarction: Slow Channel Blockade by Diltiazem Versus Beta-Adrenoceptor Antagonism by Metoprolol

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Slow channel inhibitors (calcium antagonists) and beta-adrenoceptor antagonists may theoretically protect the infarcting myocardium by different mechanisms. Thus, beta-receptor antagonism reduces the oxygen demand by the combined effects of bradycardia, decreased arterial pressure, and reduced contractility, whereas slow channel inhibition chiefly increases coronary blood flow and decreases the afterload by peripheral vasodilation. The present study was designed to assess and compare the effects of the beta-receptor antagonist metoprolol with those of the calcium channel inhibitor diltiazem on cellular damage and mechanical function in the isolated working rat heart subject to coronary artery ligation. We compared the highest concentrations of both agents that could be tolerated in this preparation: diltiazem 4×10^{-7} *M* and metoprolol 10^{-4} *M*. These concentrations were equally effective in reducing enzyme release, which was taken as an index of cellular damage, and in preserving high energy phosphate contents in the infarcting myocardium. However, the 2 agents exhibited opposite effects on coronary flow rates and mechanical function. Compared with diltiazem metoprolol reduced total coronary flow, cardiac output, and left ventricular work and efficiency immediately after coronary artery ligation. However, diltiazem even favorably influenced the mechanical performance of the isolated heart compared with that of untreated control hearts during the 60 minutes of regional myocardial ischemia. These benefits were similarly apparent when the hearts were paced to the rate of control hearts. The presumed mechanism was coronary vasodilation, because afterload increased as left ventricular power production increased in this model.

These results suggest that slow channel inhibition by diltiazem has advantages over beta-receptor antagonism by metoprolol in protecting the infarcting myocardium and that further evaluation of diltiazem in other preparations is warranted.

Modification of infarct size is currently an area of great endeavor in cardiac research.[1] Many pharmacologic and metabolic principles have been studied in the experimental animal with the aim of limiting the extent of cell necrosis caused by acute myocardial ischemia. One concept follows the hypothesis of Maroko et al.[1] that the extent of ischemic injury is related to the myocardial oxygen balance. On this basis, several studies were undertaken with beta-adrenoceptor antagonists and, more recently, slow channel inhibitors (calcium antagonists). Although both types of intervention could act directly on the heart to diminish oxygen requirements by reducing left ventricular contractile force and heart rate,[2–4] in practice the depressive effect of calcium antagonists is thought to be modified by afterload reduction with a reflex increase in sympathetic tone, so that the sinus rate rarely decreases.[5] Furthermore, calcium antagonists can exert specific therapeutic effects in concentrations that do not cause myocardial depression.[6] An additional effect of slow channel inhibitors is to further reduce oxygen demand and to increase oxygen supply to the ischemic myocardium by their peripheral and coronary artery vasodilating activity, which could result in reduced left ventricular afterload and

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improved myocardial collateral flow, respectively.[2] In contrast, there is some concern that beta-adrenoceptor antagonists, particularly noncardioselective compounds, might be associated with vasoconstrictive properties.[7]

Favorable results with experimental myocardial ischemia were reported for both beta-antagonists and calcium channel inhibitors[8–16] and extensive clinical trials are already projected. However, there is as yet no study that compares these two interventions directly under the same experimental condition. Therefore, the present investigation was designed to assess and compare the effects of beta-adrenoceptor antagonism and slow channel blockade on cellular damage and mechanical function during acute regional myocardial ischemia. For our study we chose the cardioselective beta-adrenoceptor antagonist metoprolol, reasoning that cardioselectivity should diminish the tendency of beta-antagonists to cause coronary vasoconstriction,[7] and compared it with the recently introduced slow channel inhibitor diltiazem.[12]

Methods

Perfusion model: Male Long-Evans rats (270 to 330 g) were anesthetized with ether and given 200 IU of heparin intravenously. The heart, weighing about 1 g (0.959 to 1.126 g, no significant differences between all groups), was rapidly excised and arrested in chilled perfusion fluid. After 15 minutes of retrograde preperfusion through the aorta, the working heart technique described by Neely et al.[17] was started. In this model the isolated heart is filled by the left atrium at a constant filling pressure of 10 cm H_2O and pumps spontaneously against a hydrostatic pressure load of 100 cm of water. Part of the fluid ejected from the left ventricle supplies the coronary arteries, drains into the right heart, and is collected from the pulmonary arteries as coronary flow. Aortic output at the top of the hydrostatic pressure column and coronary flow were measured by calibrated cylinders and added together for cardiac output. The perfusate used in this recirculating system was a Krebs-Henseleit bicarbonate buffer, maintained at 37°C and aerated with 95% O_2 and 5% CO_2, and contained 11 m*M* of glucose as substrate. The oxygen uptake was determined from samples taken simultaneously from the left atrial cannula and directly from the pulmonary artery measured as the oxygen tension (Radiometer, Copenhagen) and related to the coronary flow rate.[17]

Acute regional myocardial ischemia was produced as described by Kannengiesser et al.[18] The left main coronary artery was ligated with 6-0 silk by a 3/8 circle taper point needle (K-801 H, Ethicon). The stitch was placed with a small width about 2 mm below the aortic root. The coronary artery was ligated after 20 minutes of left atrial perfusion and the heart was perfused an additional 60 minutes. Pharmacologically active agents were added to the perfusate 10 minutes before ligation. Measurements of coronary flow, cardiac output, peak aortic pressure, myocardial oxygen uptake, and release of lactate dehydrogenase were taken 10 minutes before and at the time of coronary artery ligation as well as 10, 20, 40, and 60 minutes thereafter.

Enzyme release: The release of lactate dehydrogenase is a sensitive marker of myocardial cell viability loss,[19] and the pattern of release from the isolated heart is similar to that of creatine kinase.[20] We measured the arteriovenous difference[20] of lactate dehydrogenase activity at the aforementioned time intervals with a Gilford 300-V spectrophotometer, using conventional assay techniques. The cumulative rate of enzyme loss was calculated, assuming linear functions, and expressed in international units per gram wet weight of heart.

Hemodynamic measurements: Aortic pressure was measured by a Statham P23 Db pressure transducer and monitored on a Devices 2 channel M2 direct writer pen recorder. Total power production (work) of the heart was calculated as the sum of pressure and kinetic power[21] according to the formulas:

$$\text{Pressure power} = p = 0.002222 \times P_s \times CO$$

$$\text{Kinetic power} = k = 1/(432 \times 10^7) \times [d(CO)^3]/A^2 \times (T/Te)^2$$

where P_s = peak systolic pressure (mm Hg), CO = cardiac output (ml/min), d = density of perfusage (1 g/cm^3), A = internal cross-sectional area of the aortic cannula (cm^3), T = cycle time (ms), and Te = ejection time (ms). The results are expressed in millijoules per second per gram heart weight. The efficiency of mechanical power production was calculated as total power divided by oxygen uptake (J/ml O_2).

Pharmacologically active agents: The beta-adrenoceptor antagonist metoprolol (Lopressor®, Geigy)[22] was used in a concentration of 1×10^{-4} *M*. The slow channel inhibitor diltiazem (Herbesser®, Tanabe Seiyaku)[23] was used in a concentration of 4×10^{-7} *M*, which was the highest dose that did not cause complete heart block. The aforementioned concentrations chosen for each compound gave best protection against cellular damage in dose-response curves.[24,25]

Because both drugs significantly reduced the heart rate, a series of 6 hearts each was paced by the right atrium at the heart rate of control hearts (230 beats/min) in order to exclude heart rate effects on enzyme release and mechanical performance. Pacing was started immediately after administration of the drugs as soon as the heart rate dropped below 230 beats/min.

Biochemical studies: To distinguish infarcting from noninfarcting myocardium, disulfine blue dye was injected into the left atrium just prior to freeze-clamping of unpaced hearts with Wollenberger tongs, precooled to the temperature of liquid nitrogen. Samples of the midischemic and uninvolved tissue of approximately 100 mg each were analyzed for adenosine triphosphate and phosphocreatine as previously described.[26] If clear separation of stained and unstained tissue was not possible because of the timing or the angle of clamping, the hearts were discarded for biochemical analysis.

Statistical procedures: Results were expressed as means ± standard error of the mean. P values were calculated by the appropriate Student's *t* test and $p < 0.05$ was taken as significant, using 2-tailed values and corrections for unequal variances. If multiple comparisons were performed, Bonferroni's correction was applied and the level of significance was raised accordingly.

Results

Effects of Metoprolol and Diltiazem on the Working Rat Heart Before Coronary Artery Ligation

The administration of metoprolol and diltiazem reduced the heart rate of the working heart from 244 ± 8 to 168 ± 14 beats/min ($p < 0.001$) and from 256 ± 10 to 212 ± 9 beats/min ($p < 0.05$), respectively. Diltiazem produced no change in cardiac output (56.2 ± 1.2 versus 54.0 ± 1.2 ml/min after diltiazem), whereas with metoprolol the cardiac output decreased from 58.1 ± 2.0

TABLE I Effects of Metoprolol and Diltiazem on Coronary Flow, Oxygen Uptake, and Left Ventricular Power Production and Efficiency Before and After Coronary Artery Ligation

Ligation	Control (n = 10)	Metoprolol Nonpaced (n = 10)	Metoprolol Paced (n = 6)	Diltiazem Nonpaced (n = 12)	p vs Nonpaced Metoprolol	Diltiazem Paced (n = 6)	p vs Paced Metoprolol
Coronary flow (ml/min)							
BL	15.0 ± 0.7	13.2 ± 0.4	13.9 ± 0.5	14.2 ± 0.6	NS	13.7 ± 0.3	NS
Pre	15.0 ± 0.7	11.8 ± 0.3	11.8 ± 0.3*	15.8 ± 0.6	<0.001	16.9 ± 0.4	<0.001
10′	7.6 ± 0.2	6.2 ± 0.5†	6.4 ± 0.3‡	8.6 ± 0.8	<0.025	9.3 ± 0.3*	<0.001
60′	8.1 ± 0.2	6.6 ± 0.5†	7.4 ± 0.4	8.7 ± 0.7	NS	9.8 ± 0.6	<0.01
Oxygen uptake (μl/min/g)							
BL	158 ± 5	155 ± 5	147 ± 4	164 ± 6	NS	159 ± 5	NS
Pre	163 ± 4	136 ± 3*	134 ± 4*	166 ± 6	<0.001	187 ± 8‡	<0.001
10′	93 ± 5	72 ± 6†	74 ± 2‡	95 ± 8	NS	106 ± 3	<0.001
60′	87 ± 3	75 ± 8	80 ± 3	96 ± 7	NS	106 ± 6‡	<0.01
Left ventricular power production (mJ/g/s)							
BL	15.49 ± 0.30	14.85 ± 0.56	13.97 ± 0.76	14.14 ± 0.44	NS	14.64 ± 0.77	NS
Pre	15.41 ± 0.35	14.18 ± 0.44	13.27 ± 1.07	14.50 ± 0.53	NS	13.47 ± 0.77	NS
10′	7.09 ± 0.33	3.92 ± 0.66*	5.28 ± 0.60†	7.28 ± 0.51	<0.001	8.00 ± 0.55	<0.01
60′	4.91 ± 0.73	4.40 ± 0.63	5.71 ± 0.45	7.10 ± 0.35†	<0.001	8.79 ± 0.65‡	<0.005
Efficiency (J/ml O_2)							
BL	5.94 ± 0.23	5.49 ± 0.31	5.67 ± 0.18	5.20 ± 0.16	NS	5.52 ± 0.17	NS
Pre	5.76 ± 0.23	6.25 ± 0.17	5.92 ± 0.36	5.26 ± 0.14	<0.001	4.33 ± 0.17	<0.01
10′	4.63 ± 0.28	3.19 ± 0.34‡	4.23 ± 0.42	4.78 ± 0.10	<0.001	4.53 ± 0.23	NS
60′	3.46 ± 0.45	3.49 ± 0.31	4.27 ± 0.34	4.62 ± 0.30	<0.02	4.96 ± 0.20‡	NS

* $p < 0.001$, † $p < 0.02$, ‡ $p < 0.01$, versus control.
BL = baseline values, predrug; Pre = preligation; 10′, 60′ = minutes after ligation; NS = not significant ($p > 0.025$).
Values are mean ± standard error of the mean for number of hearts in brackets.

ml/min to 48.7 ± 1.7 ml/min ($p < 0.001$). This decrease apparently was the result of a reduced heart rate because it was abolished by supraventricular pacing (55.8 ± 2.7 versus 52.7 ± 3.8 ml/min after metoprolol) at a rate of 230 beats per min, which was the heart rate of untreated control hearts after coronary artery ligation.

Diltiazem increased the coronary flow from 14.2 ± 0.6 to 15.8 ± 0.6 ml/min ($p < 0.001$). In contrast to diltiazem and possibly as an effect of reduced oxygen requirements, metoprolol decreased the coronary flow from 13.2 ± 0.4 to 11.8 ± 0.3 ml/min ($p < 0.005$). Similar results for coronary flow rates, oxygen uptake, and left ventricular work and efficiency were obtained in the paced groups. However, during the elevated heart rate an increase in oxygen uptake from 159 ± 5 to 187 ± 8 μl/min/g ($p < 0.01$) was followed by a reduction in efficiency from 5.52 ± 0.17 to 4.33 ± 0.17 J/ml O_2 ($p < 0.005$) in the diltiazem group. It may be speculated that this effect was the result of an intrinsic limitation of this isolated model for further vasodilation, because the coronary flow accounts for about one third of the cardiac output ejected from the left ventricle.

Effects of Metoprolol and Diltiazem on the Rat Heart After Coronary Artery Ligation

Coronary flow (Table I): Ligation of the left main coronary artery reduced the total coronary flow rate in untreated control hearts by 49% from 15.0 ± 0.6 to 7.6 ± 0.2 ml/min after 10 minutes. In the presence of metoprolol, the coronary flow decreased from 11.8 ± 0.3 to 6.2 ± 0.5 ml/min (47%) and with diltiazem from 15.8 ± 0.6 to 8.6 ± 0.8 ml/min (46%) ($p < 0.025$ versus metoprolol). Hearts perfused with metoprolol generally had significantly lower flow rates than control hearts or hearts treated with diltiazem. It should be emphasized that these values of coronary flow refer to total flow, that is, the sum of ischemic and nonischemic zones.

Mechanical function (Fig. 1): To assess mechanical function, we measured cardiac output and calculated left ventricular work. In control hearts cardiac output decreased 45% from 59.5 ± 1.2 to 32.8 ± 1.2 ml/min immediately after coronary ligation and progressively declined over the ensuing 60 minutes of acute regional myocardial ischemia. In hearts perfused with metoprolol cardiac output was initially reduced 64% to 17.5 ± 2.5 ml/min ($p < 0.001$ versus control), but was then maintained at that level, so that 60 minutes after ligation the metoprolol-treated and control hearts had similar cardiac outputs. With diltiazem, cardiac output first decreased similarly to control by 43% to 30.9 ± 1.5 ml/min. However, these hearts showed no trend as did control hearts to go into cardiac failure, which in this model is defined as zero aortic output. Throughout the period of acute ischemia diltiazem maintained higher cardiac outputs than did metoprolol ($p < 0.001$).

Right atrial pacing to the heart rate of control hearts increased cardiac output and left ventricular work in both drug-treated groups, yet the differences remained the same. However, pacing of diltiazem-treated hearts for 60 minutes after coronary artery ligation resulted

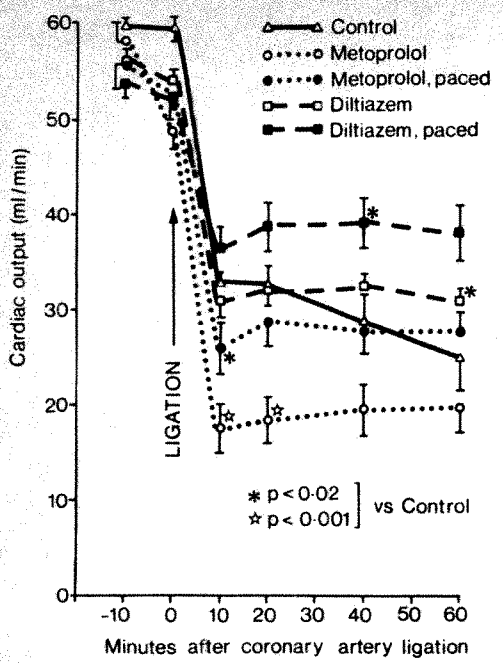

FIGURE 1. Effect of metoprolol 10^{-4} *M* (n = 10, paced n = 6) and diltiazem 4×10^{-7} *M* (n = 12, paced n = 6) on cardiac output. Diltiazem maintained higher cardiac output compared with metoprolol in unpaced ($p < 0.001$) as well as paced ($p < 0.01$) hearts throughout the duration of regional myocardial ischemia. Control n = 10.

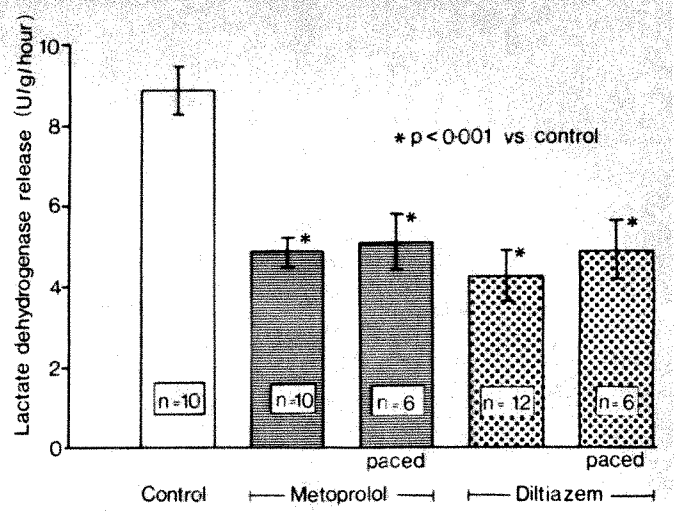

FIGURE 2. Cumulative release of lactate dehydrogenase over 60 minutes after coronary ligation with metoprolol (1×10^{-4} *M*) and diltiazem (4×10^{-7} *M*) in paced and unpaced hearts. The 2 compounds were equally effective in reducing enzyme release.

in significantly higher cardiac output and left ventricular work compared with control hearts (Table I).

Efficiency of cardiac work (Table I): Enhanced mechanical function resulting from diltiazem could increase oxygen demand, which theoretically could be deleterious to the ischemic heart. Therefore, we measured oxygen uptake and related it to left ventricular work, thereby calculating the efficiency of cardiac work. Coronary artery ligation reduced the efficiency of work in control hearts from 5.76 ± 0.23 to 4.63 ± 0.28 J/ml O_2 10 minutes after ligation and to 3.46 ± 0.45 J/ml O_2 60 minutes after ligation. Metoprolol either left the efficiency unchanged or decreased it (10 minutes after ligation, unpaced hearts). Diltiazem was associated with significantly higher efficiency values than metoprolol. However, this difference was not apparent if hearts were paced at equal heart rates.

Enzyme release (Fig. 2): In control hearts, production of acute regional myocardial ischemia resulted in a release of lactate dehydrogenase of 8.88 ± 0.60 U/h/g. This amount was reduced by about half by both metoprolol 1×10^{-4} *M* to 4.85 ± 0.38 U/h/g ($p < 0.001$) and by diltiazem 4×10^{-7} *M* to 4.25 ± 0.62 U/g/h ($p < 0.001$), reflecting preservation of cell integrity. Pacing of these hearts to the heart rate of control hearts (230 beats/min) did not alter this benefit and excluded a low heart rate as the mechanism of protection against the effects of ischemia.

To disclose possible mechanisms of protection the release of enzymes over the duration of the experiments is shown in Figure 3. The pattern of release appeared identical in all groups, therefore ruling out a major involvement of washout effects.

Tissue high energy phosphate content (Table II): Production of regional myocardial ischemia resulted in substantial depletion of high energy phosphates in the infarcting myocardium, with a decrease in adenosine triphosphate values to 0.60 ± 0.05 μmol/g fresh weight, but it also reduced adenosine triphosphate in the noninfarcting tissue (2.83 ± 0.30 μmol/g) as compared with control hearts without coronary ligation (3.40 ± 0.13 μmol/g) or the values found in retrograde perfused, "nonworking" hearts (5.08 ± 0.22 μmol/g). The contents of high energy phosphates in the infarcting myocardium were significantly preserved by both metoprolol and diltiazem. Of interest was that better mechanical function of hearts perfused with diltiazem was also associated with a higher adenosine triphosphate value (3.70 ± 0.13 μmol/g, $p < 0.05$) in the noninfarcting zone. It should be noted that the separation of tissue into ischemic and nonischemic zones is arbitrary, because of the graduation of coronary flow reduction to various

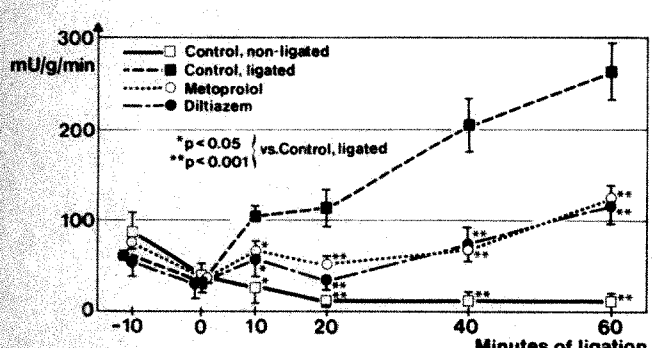

Figure 3. Release of lactate dehydrogenase over the time course of the experiments in coronary artery ligated (n = 10) and nonligated control hearts (n = 10) and hearts treated with metoprolol (n = 10) and diltiazem (n = 12).

TABLE II Tissue High Energy Phosphate Contents in the Infarcting and Noninfarcting Myocardium

	Adenosine Triphosphate (μmol/g Fresh Weight)		Phosphocreatine (μmol/g Fresh Weight)	
	Noninfarcting	Infarcting	Noninfarcting	Infarcting
Preperfusion period, nonworking (n = 5)	5.08 ± 0.22	. . .	7.25 ± 0.41	. . .
Control, working heart nonligated (n = 10)*	3.40 ± 0.13	. . .	4.03 ± 0.30	. . .
Control, ligated (n = 9)	2.83 ± 0.30	0.60 ± 0.05	4.01 ± 0.46	1.21 ± 0.11
Metoprolol (n = 6)	3.38 ± 0.29	1.08 ± 0.17†	3.95 ± 0.28	1.72 ± 0.23†
Diltiazem (n = 6)	3.70 ± 0.13†	0.97 ± 0.12‡	3.70 ± 0.27	1.46 ± 0.14

* Data from Kannengiesser et al.[18]
† $p < 0.05$.
‡ $p < 0.01$ versus control, ligated.
Values are mean ± standard error of the mean.

zones of the heart in this model.[18] However, even considerable admixture of ischemic and nonischemic tissue in the assay samples could not explain the more beneficial effect of diltiazem than metoprolol on adenosine triphosphate levels. Only metoprolol improved phosphocreatine values in the ischemic zone.

Discussion

Cellular damage: The present investigation demonstrated that the beta-adrenoceptor antagonist metoprolol and the slow channel inhibitor diltiazem exert substantial protection against cellular damage on acutely infarcting myocardium. Similar results have been obtained for other compounds in each drug group,[8–16] although not consistently.[27–29] In the concentrations used, both interventions were equally effective in protecting myocardial cell integrity as assessed by enzyme loss in our preparation, and in addition preserved adenosine triphosphate in the infarcting tissue. Metoprolol, in addition, maintained phosphocreatine levels (Table II). However, the 2 agents exhibited opposing effects on the mechanical function of the heart after coronary ligation. Compared with diltiazem metoprolol caused deterioration of cardiac output and left ventricular work and efficiency immediately after production of acute myocardial ischemia.

Effect on mechanical function: Some studies in larger animals[30] have not revealed a depressant effect of beta-adrenoceptor antagonism on the mechanical function of the heart, but the compound used was practolol, which showed little cardiodepressant effect in some patient studies. A possible explanation for the relative absence of cardiodepressant effects by practolol is the intrinsic sympathomimetic activity that metoprolol does not possess. The concentration of metoprolol we used was probably higher than comparable doses of other beta-adrenoceptor antagonists used in most intact animal studies. In patients with acute infarction, intravenous metoprolol has also been used without precipitating left ventricular failure,[31] but the patients initially had no clinical features of congestive heart failure, and therefore probably had relatively small infarcts. Ligation of the left main coronary artery in rats results in an infarct involving almost all of the free wall of the left ventricle[32] and with a mean overall reduction of coronary flow to 57% of the preligation value.[18] Therefore, the more extensive size of the ischemic zone in this preparation probably produced a more significant cardiac deterioration than that found in most patients with acute infarction.

Improvement of the mechanical function of the heart mediated by diltiazem or other slow channel inhibitors has also been demonstrated in ischemic-reperfused preparations,[33–35] and has been further confirmed in the case of nifedipine by measurements of enhanced regional myocardial contractility in the ischemic myocardium of larger animals.[36] The effect on mechanical performance is considered to be related to the ability of these compounds to prevent deleterious intracellular calcium accumulation which can impair left ventricular contractile force and relaxation,[37] but improved coronary perfusion to the ischemic zone is likely to be another important factor.[36,38] Verapamil, in contrast, appears to depress regional myocardial contractility in the ischemic but not the nonischemic myocardium, whereas propranolol depresses both normal and ischemic myocardium.[39]

Preservation of cell integrity: A variety of mechanisms have already been proposed for the reduction of cellular damage in the acutely infarcting myocardium by beta-receptor antagonists and slow channel inhibitors.[3,5,8,12] Our experiments show that protection can be achieved when heart rate is not reduced.

Severity of cellular damage has been assessed by release of lactate dehydrogenase and the tissue content of high energy phosphates. It has to be noted that phosphocreatine, increased in the ischemic zone only by metoprolol, cannot be related to the extent of enzyme release[40] in contrast to the level of adenosine triphosphate.[41] It may be speculated that the elevated adenosine triphosphate content achieved by both metoprolol and diltiazem in ischemic myocardium could represent a specialized pool to which Bricknell and Opie[42] attributed a role in protecting the cell membrane.

Myocardial perfusion: In addition to the beneficial effects of diltiazem on the calcium homeostasis in the ischemic myocardium, its vasodilating activity has to be considered as a mechanism of protection.[36,38] Dilti-

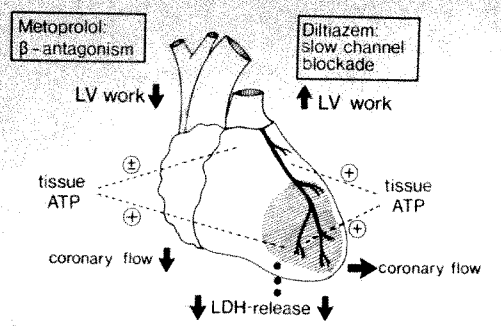

FIGURE 4. Comparative effects of metoprolol and diltiazem on acutely infarcting myocardium. Results are based on comparisons with control hearts in Tables I and II. ATP = adenosine triphosphate; LDH = lactic dehydrogenase; LV = left ventricle.

azem causes an increase in the blood flow in the peripheral zone of regional myocardial ischemia in the pig model.[43,44] Because no evidence for a coronary "steal" phenomenon[43–45] with diltiazem has been reported (in contrast to nifedipine[27]), one may suppose from our experiments that there was a redistribution, which was not clearly detectable by measuring the total coronary flow rate. By this, oxygen supply to the ischemic tissue would be improved and tissue acidosis diminished through washout of lactate and hydrogen ions. Excess hydrogen ions not only interfere with key reactions of metabolic pathways,[46] but also represent another factor that has been associated with impairment of the contractile function.[47].

Even though metoprolol exhibited reduced total coronary flow rates in our model, we cannot completely exclude a favorable redistribution of flow to the ischemic zone as found in the pig model.[48] A reduced washout of enzymes is possible in the case of metoprolol, so that enzyme release was falsely low; this sequence is rendered unlikely by increased values for high energy phosphates in the infarcting tissue. In addition, no facilitated washout is apparent for diltiazem (Fig. 2). Therefore, equal protection of cell integrity in the presence of significantly different flow rates suggests that mechanisms other than perfusion effects are involved in mediating preservation of ischemic myocardium. However, the opposing effects on mechanical function may possibly be related to the degree of myocardial perfusion.

Critique of the model: The isolated working rat heart with coronary artery ligation is a model with both advantages and disadvantages. The dynamic function of the heart can be studied under reproducible and controllable conditions,[18] whereas the severity of cellular damage induced by coronary artery ligation can be measured continuously and accurately by enzyme release.[20] A limitation of this preparation is that it fails to allow physiologic interaction of the heart with the peripheral circulation. The preparation is severed from the autonomic nervous system, quite unlike the situation in patients with infarction. The results obtained with this model cannot directly be extrapolated to the human heart, because heart rate, cardiac output, and coronary flow rates of the isolated rat heart are not comparable to those in man. The situation in any animal model when healthy coronary arteries are abruptly ligated may not be relevant to the much more complex coronary artery anatomy in patients when occlusive disease can antedate acute infarction by many years.

Another outstanding question is whether the beneficial effects of diltiazem administration before coronary artery ligation could also be achieved after the onset of the infarction process. However, most of the interventions initially applied before coronary artery occlusion[1] have also been effective within the first hours after coronary occlusion.[3]

The experimental concentrations of the 2 potentially cardioprotective agents are also open to criticism. With diltiazem, therapeutic concentrations in patients may reach 3×10^{-7} g/ml or 7.3×10^{-7} *M*.[5] Similar concentrations inhibit smooth muscle excitation coupling in the coronary arteries of the pig[2] and increase spontaneous cycle length in the isolated sinoatrial node in the rabbit.[5] Hence, the concentration (4×10^{-7} *M*) used in this study may well be of therapeutic importance in clinical practice. With metoprolol, a relatively large dose (10^{-4} *M*) was used that is well above the effective blood level of about 10^{-7} *M*.[49] At such high concentrations, cardioselectivity might well have been lost, hence tending to reduce coronary flow by an unopposed alpha-mediated vasoconstriction. However, because our study was based on a comparison of 2 similarly potent protective concentrations, 10^{-4} *M* of metoprolol was required to be as effective as 4×10^{-7} *M* of diltiazem.[23,24] This concentration of metoprolol was also required to antagonize isoproterenol 10^{-6} *M*. The local concentration of norepinephrine in ischemic myocardium is likely to be about 10^{-6} *M*.[40] At such very high concentrations, effects other than beta-antagonism, such as membrane protection, are likely to be relevant.

Such comparisons apply strictly to the isolated heart. In patients with acute myocardial infarction, circulating catecholamine concentrations (largely norepinephrine) are increased to about 5×10^{-9} *M*[50]; such concentrations of norepinephrine fail to increase enzyme release from the isolated rat heart.[40] Hence, our data may possibly have application in acute myocardial infarction even in the absence of added catecholamine stimulation.

Conclusion: The present study demonstrates that beta-adrenoceptor antagonism by metoprolol at large doses and slow channel inhibition by diltiazem at apparently therapeutic doses are equally effective in reducing cellular damage in the acutely infarcting myocardium but that there are opposing effects on the mechanical function of the heart. Diltiazem offered substantial cardioprotection in the presence of significantly better mechanical performance than metoprolol. Whereas metoprolol reduced cardiac output and left ventricular work compared with untreated control hearts, these variables appear to be influenced in a favorable way by diltiazem. Although our results were obtained in an isolated, perfused rat heart model, the principles involved could be of considerable importance in a clinical setting. Patients with acute myocardial infarction often have restricted ventricular function,

especially when the infarct is large, as in our model.[51] Further myocardial depression by beta-receptor antagonism could initiate cardiac decompensation and result in cardiogenic shock, whereas our studies raise the expectation that diltiazem could improve the mechanical function possibly by facilitating blood flow to the ischemic zone.

Although conclusions drawn from diltiazem may not apply to other slow channel inhibitors and evidence indicates that further experimental data in other models are required, both theoretical and experimental data suggest that slow channel blockade could become a more promising therapeutic approach than beta-adrenoceptor antagonism in minimizing myocardial infarct size (Fig. 4).

Acknowledgment

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Inhibition of Hypoxic Pulmonary Vasoconstriction By Nifedipine

THOMAS KENNEDY, MD, MPH and WARREN SUMMER, MD

Nifedipine is a potent slow channel calcium antagonist and systemic vasodilator recently reported to attenuate hypoxic pulmonary vasoconstriction in man. Other systemic vasodilators have also been shown to attenuate hypoxic pulmonary vasoconstriction, but their effects in some species may be mediated by reflex beta-adrenergic discharge. We evaluated the effect of nifedipine on the relation between pulmonary arterial pressure and blood flow during hyperoxia (inspired partial pressure of oxygen [PO_2] 200 mm Hg) and hypoxia (inspired PO_2 50 mm Hg) in denervated ventilated pig lungs perfused in situ with the animal's own blood. Ten lungs were ventilated with alternating 15 minute periods of hyperoxia and hypoxia. Hypoxia shifted the pulmonary artery pressure (x axis)-blood flow (y axis) relationship to the right and decreased its slope, indicating vasoconstriction. Nifedipine, given as a 0.1, 1, or 10 μg/kg bolus into the pulmonary artery, caused a dose-dependent reduction of hypoxic pulmonary vasoconstriction. It is concluded that nifedipine is a potent pulmonary vasodilator acting locally within the lung and that it might be useful in the therapy of hypoxic pulmonary hypertension from chronic lung disease in man.

Pulmonary hypertension and resulting cor pulmonale account for 7 to 10% of all heart disease in the United States.[1] Probably the most important cause of cor pulmonale is hypoxic pulmonary hypertension associated with disorders such as chronic bronchitis and emphysema, bronchiectasis, cystic fibrosis, kyphoscoliosis, and chronic mountain sickness. The recommended therapy for hypoxic pulmonary hypertension is sufficient oxygen to relieve alveolar hypoxia and systemic hypoxemia.[2] However, supplemental oxygen is not always effective in relieving the elevated pulmonary artery pressure in these disorders[3] and is unquestionably expensive and inconvenient.

Recently, Simonneau et al.[4] demonstrated that nifedipine, a potent slow channel calcium antagonist and systemic vasodilator, inhibits hypoxic pulmonary vasoconstriction in patients with acute respiratory failure without deleterious effects on arterial oxygen saturation or delivery. Muramoto et al.[5] reported similar findings in a group of 9 patients with clinically stable chronic obstructive pulmonary disease. In their study subjects experienced an improvement in cardiac output and pulmonary vascular resistance at rest and during exercise, with a shift in pressure-flow curves to the right, indicating a decrease in pulmonary pressure at similar levels of cardiac output occurring when subjects were treated with nifedipine as opposed to placebo. Arteriovenous oxygen content decreased whereas arterial oxygen saturation did not change.

These results indicate that nifedipine is potentially useful as a vasodilator to reduce the afterload of the right ventricle in cor pulmonale resulting from hypoxic pulmonary hypertension, but shed no light on whether nifedipine acts locally within the lung or indirectly through the sympathetic nervous system. Minoxidil reduces hypoxic pulmonary hypertension, but its effect in hypoxic cattle is prevented by beta-adrenergic blockade.[6] Nifedipine also stimulates a reflex sympathetic discharge.[7,8] To determine whether nifedipine locally or reflexly inhibits hypoxic pulmonary hypertension, we investigated the ability of increasing doses of nifedipine to reverse the pulmonary hypoxic response in isolated perfused pig lungs void of any sympathetic innervation.

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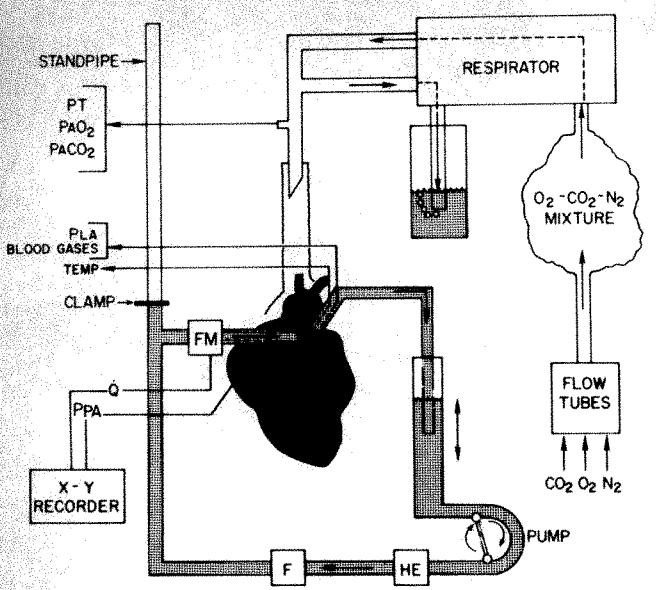

FIGURE 1. Diagram of perfusion apparatus for pig lung. F = flow; FM = flow meter; HE = heat exchanger; PLA = left atrial pressure; PPA = pulmonary artery pressure; PT = tracheal pressure.

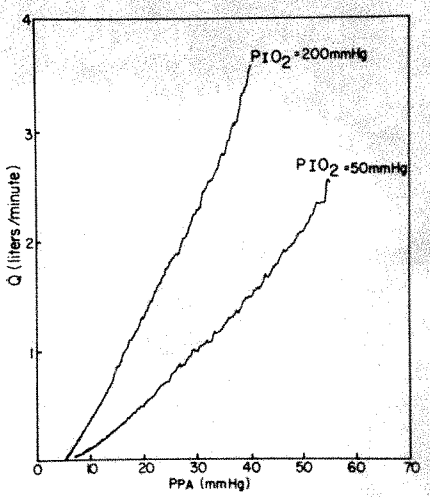

FIGURE 2. Typical pulmonary pressure (Ppa)-flow (Q̇) curves during hyperoxia (PIO_2 = 200 mm Hg) and hypoxia (PIO_2 = 50 mm Hg).

Methods

Experimental preparation: The pig was chosen as the experimental animal because its pulmonary circulation responds vigorously to hypoxia.[9] Pigs weighing 20 to 40 kg were anesthetized with intravenous pentobarbital sodium and ventilated through a tracheal cannula with room air by a respirator. After mid-sternal thoracotomy the animal was given 10,000 U of heparin intravenously, the left atrium was cannulated, and the animal was then bled a volume of approximately 1,000 ml into a Plexiglas® reservoir (Fig. 1). This volume of blood was supplemented with 6% dextran in normal saline solution to yield a total perfusate volume of 1,500 ml. The pulmonary artery was then cannulated and the root of the aorta was tied off. During perfusion, blood entered the left atrium, drained by gravity into the reservoir, and was then pumped with a roller pump (Sarns model 3500) through a heat exchanger, blood filter, and electromagnetic flow probe to the pulmonary artery. Except during pressure-flow determinations, blood flow was constant at 1.0 liter/min. Pulmonary artery and left atrial pressure was measured with strain gauges zero-referenced to the level of the right atrioventricular valve. Left atrial pressure was maintained at −20 mm Hg by adjusting the level of the reservoir. After perfusion was begun, the lungs were ventilated with a normoxic normocapnic gas mixture at a rate of 6 to 7 breaths/min and a tidal volume of 400 ml. End-expiratory tracheal pressure was kept at 3 to 4 cm of water to prevent alveolar collapse. Airway oxygen and carbon dioxide tensions were measured with gas analyzers (Beckman). Blood temperature was kept between 38.5 and 39.5°C. Blood gas tensions and pH were measured by standard electrode techniques (Radiometer BMS3 MK2). Blood PCO_2 was 35 to 40 mm Hg and pH 7.35 to 7.45.

Hyperoxia and hypoxia: After a stabilization period of 60 minutes, the lungs were exposed alternately to hyperoxic and hypoxic gas mixtures. During hyperoxia the inspired gas consisted of 38.2% oxygen, 5.4% carbon dioxide, and 66.4% nitrogen. During hypoxia it consisted of 7% oxygen, 5.4% carbon dioxide, and 87.6% nitrogen. This level of hypoxia was chosen because in the pig it causes maximal steady state pulmonary vasoconstriction.[9] When pulmonary artery pressure stabilized, the pulmonary artery pressure-flow relation was determined by stopping ventilation in end-expiration, increasing pump flow to fill the standpipe (Fig. 1) and, when pulmonary artery pressure was stable, suddenly stopping the pump to allow blood to flow by gravity from the standpipe through the lungs into the reservoir until zero flow was achieved. During this procedure, an x-y recorder was used to record the relation between pulmonary artery pressure (x) and flow (y). Measurement of the relation between pulmonary artery pressure and blood flow has previously been used by a number of investigators[10–12] to demonstrate the state of pulmonary vascular resistance over a wide range of possible blood flows, thus avoiding possible pitfalls of measuring a single value of pulmonary artery pressure at constant flow. Figure 2 illustrates typical curves recorded during normoxia and hypoxia. During hypoxia, the curve is shifted to the right and decreased in slope, indicating vasoconstriction. Changes in these pressure-flow relations were quantified by determining the pulmonary artery pressure at a flow of 1 liter/min directly from the record curve.

Nifedipine administration: Two groups of animals (n = 5 in each) were studied. All lungs underwent 300 minutes of perfusion. Pulmonary artery pressure-flow relations were determined at the end of each period of hyperoxia and hypoxia. After determination of a curve, the inspired gas mixture was changed and time was allowed for stabilization of pulmonary artery pressure before another curve was recorded. Generally, stabilization occurred within 15 minutes. The experimental group received nifedipine into the pulmonary artery in injections of 0.1, 1, and 10 μg/kg at perfusion times of 120, 180, and 240 minutes. Nifedipine in a concentration of 100 μg/ml was prepared under conditions of reduced light in a vehicle consisting of 14 ml of polyethylene glycol, 22 ml of absolute ethanol, and 64 ml of water, and was diluted with appropriate volumes of vehicle to achieve an injection volume of 0.1 ml/kg. The control group received injections of 0.1 ml/kg of vehicle alone into the pulmonary artery at perfusion times of 120, 180, and 240 minutes. Blood pH was checked after each administration of drug to confirm that it had not changed.

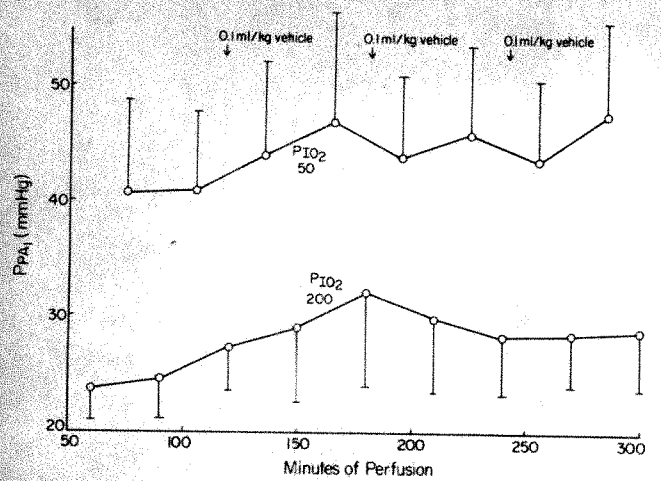

FIGURE 3. Pulmonary artery pressure of control animals (n = 5) at a blood flow of 1 liter/min (Ppa_1) during alternating periods of hyperoxia (PIO_2 = 200 mm Hg) and hypoxia (PIO_2 = 50 mm Hg) ventilation. **Open circles** represent mean PPa ± 1 standard error of the mean.

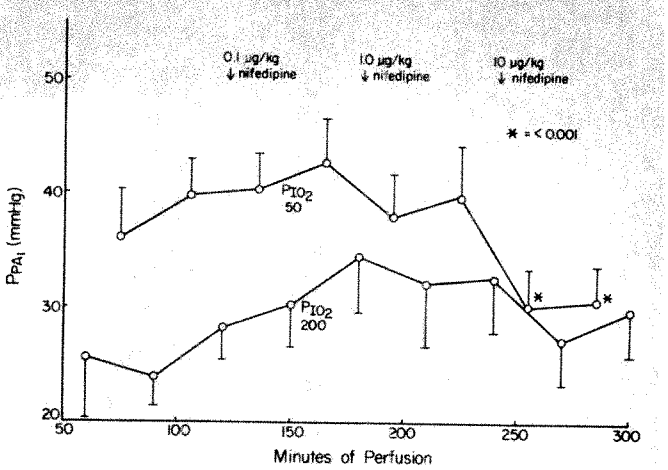

FIGURE 4. Pulmonary artery pressure of nifedipine-treated animals (n = 5) at a blood flow of 1 liter/min (Ppa_1) during alternating periods of hyperoxia (PIO_2 = 200 mm Hg) and hypoxia (PIO_2 = 50 mm Hg) ventilation. **Open circles** represent mean PPa ± 1 standard error of the mean.

Values for pulmonary artery pressure at a flow of 1 liter/min (Ppa_1) during hyperoxia and hypoxia for control and experimental animals and differences between Ppa_1 for each hyperoxic and its subsequent hypoxic value for control and experimental animals were compared using a 2-way analysis of variance. When F ratios achieved a 0.05 level of significance, a protected least significant difference was computed according to the method of Fisher.[13]

Results

Control versus nifedipine: Results for control animals are shown in Figure 3, in which mean values of pulmonary artery pressure at a blood flow of 1 liter/min (Ppa_1) for the 5 animals are plotted for each set of hyperoxic and hypoxic curves determined during the 300 minute perfusion. Both hypoxic and hyperoxic responses tended to reach a relative plateau after 120 minutes. Mean values of pulmonary artery pressure at a flow of 1 liter/min during hyperoxia and hypoxia for nifedipine-treated animals are shown in Figure 4. A decrease in mean pulmonary artery preasure at a flow of 1 liter/min was not seen until after the 1.0 µg/kg dose of nifedipine. After the 10 µg/kg dose there was nearly complete abolition of hypoxic vasoconstriction with some transient decrease in mean Ppa_1 during hyperoxia as well.

Mean inhibition of the hypoxic pressor response (mean ΔPpa_1) as a function of dose of nifedipine (Fig. 5). For each animal, ΔPpa_1 was determined as the difference between pulmonary artery pressure at a blood flow of 1 liter/min during hyperoxia at perfusion times of 90, 150, 210, and 270 minutes, and the subsequent stable pulmonary artery pressure at 1 liter/min flow during hypoxia at perfusion times of 105, 165, 225, and 285 minutes, respectively, for control and increasing doses of nifedipine. Thus ΔPpa_1 corresponds to the difference between the last hyperoxic and hypoxic response during each study period before subsequent administration of the next larger dose of drug and was chosen to allow the respective doses of drug to circulate within the perfusion system so that drug effect could stabilize. The mean ΔPpa_1 of control animals remained stable over all 4 study periods. The mean ΔPpa_1 for nifedipine-treated animals decreased progressively with logarithmically increasing doses of drug, so that at a dose of 1 µg/kg there was 50% inhibition of the hypoxic response, and at a dose of 10 µg/kg nearly complete inhibition occurred.

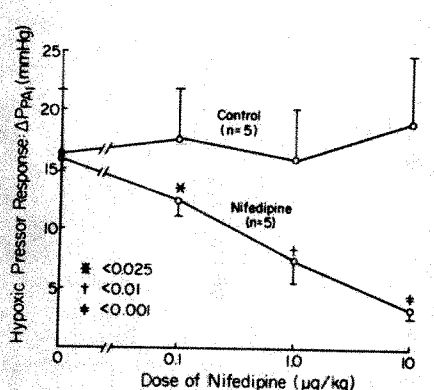

FIGURE 5. Hypoxic pressor response (ΔPpa_1) in control (n = 5) and nifedipine-treated (n = 5) animals as a function of dose of nifedipine. Each **open circle** represents mean ΔPpa_1 ± 1 standard error of the mean.

Discussion

Hypoxia is an effective and consistent stimulus to pulmonary hypertension.[14] However, debate still exists as to whether hypoxia exerts its effects directly on pulmonary vascular smooth muscle or indirectly through mediator release within the lung.[15] The results of our study indicate that nifedipine is a potent inhibitor of the pulmonary hypoxic response, independent of the

reflex adrenergic discharge. However, we cannot conclude where within the lung itself nifedipine's action is located.

Effect of slow channel calcium antagonists on pulmonary hypoxic response: Blockade of the pulmonary hypoxic response by slow channel calcium antagonists was first reported in 1976 by McMurtry et al.,[16] who used verapamil to inhibit hypoxic pulmonary hypertension in isolated rat lungs. These investigators suggested that hypoxia might act directly to depolarize pulmonary vascular smooth muscle, and that verapamil inhibited the transmembrane flow of calcium into the cell and prevented activation of the contractile machinery. Where and how this supposed inhibition of transmembrane calcium flux works in vascular smooth muscle is unclear. It is even unclear whether verapamil and nifedipine affect calcium flux in the same way. In cardiac muscle, where contraction is associated with changes in calcium flux initiated by cellular membrane depolarization, verapamil alters the kinetics of calcium flux, whereas nifedipine affects total calcium conductance, presumably by differential effects on the two gates of the calcium channel of cardiac tissue.[17] In vascular smooth muscle, however, contraction was recently found to be dependent on pharmacomechanical coupling, that is, contraction that is induced by the binding of an exogenous agent such as norepinephrine to a receptor, precipitating changes in calcium flux not necessarily associated with changes in transmembrane potential.[18] We are not aware of any work conclusively pointing to differential sites of action of nifedipine and verapamil on calcium flux in vascular smooth muscle. Until such work is available, the demonstration that both nifedipine and verapamil inhibit the pulmonary hypoxic response does not add to our basic understanding of the potential subcellular mechanisms in smooth muscle that might be operative in hypoxic pulmonary vasoconstriction.

Site and mechanism of inhibition of pulmonary hypoxic response: It is not even certain that slow channel calcium antagonists are working only at the level of vascular smooth muscle to inhibit the pulmonary hypoxic response. It was previously suggested that the pulmonary hypoxic response is induced by mast cell release of vasoactive substances,[19,20] and mast cells are strategically dispersed along the course of the pulmonary resistance vessels.[21] The observation that both nifedipine and verapamil inhibit pulmonary hypertension in cat lobes infused with a stable prostaglandin endoperoxide[22] indicates that these agents are able to block pharmacomechanical coupling in pulmonary vascular smooth muscle. In preliminary in vitro experiments, some investigators[23] claimed that nifedipine blocks the release of platelet-activating factors and slow reactive substances, and reduces release of acid phosphatase and glucuronidase from human polymorphonuclear leukocytes induced by ionophore, zymozan, or zymozan-complement complexes. If these results are confirmed and shown true for mast cells as well, it is possible that nifedipine might be blocking the calcium-dependent release of some vasoactive substance released locally within the lung in response to hypoxia.

Clinical implications: Regardless of the mechanism of subcellular action, the demonstration that a vasodilator works locally within the lung to attenuate hypoxic pulmonary hypertension may be considerably important in predicting any ultimate benefit to patients with pulmonary hypertension given the agent as therapy. Nitroglycerin was explored as a vasodilator in patients with pulmonary hypertension from chronic obstructive pulmonary disease, and was demonstrated to decrease mean pulmonary artery pressure.[24] However, nitroglycerin accomplishes this only by altering venous capacitance to decrease right ventricular preload, without affecting pulmonary vascular resistance. Thus, a decrease in mean pulmonary artery pressure is achieved at the expense of a decrease in cardiac output and oxygen delivery. Bishop et al.[25] recently reported that both nifedipine and minoxidil inhibit the pulmonary hypoxic response in intact dogs. However, minoxidil was previously demonstrated[6] to lose its effectiveness as a pulmonary vasodilator in hypoxic cattle after beta-adrenergic blockade. Despite the fact that nifedipine also elicits a reflex beta-adrenergic discharge,[7,8] our results clearly document that pulmonary vasodilation from nifedipine in a denervated pig lung is void of any potential for reflex sympathetic activity. Thus, if the human circulation responds similarly to the hypoxic bovine pulmonary circulation, subjects with lung disease might not have pulmonary vasodilation from minoxidil if they are also receiving cardioselective beta-blockers or centrally acting antihypertensive agents that decrease sympathetic outflow, but their response to nifedipine might be expected to remain intact.

To be useful in a clinical setting, nifedipine would have to be proved efficacious in producing a decrease in pulmonary vascular resistance without markedly altering redistribution of blood to poorly ventilated regions so as to not worsen hypoxemia. We were unable to address this question because the perfusate reservoir of our preparation was open to air, but in a recent report, Bishop et al.[25] found that nifedipine increased venous admixture in intact dogs. However, Simonneau et al.[4] found only a slight (45 ± 2 to 42 ± 2 mm Hg) although statistically significant change in arterial PO_2 in a group of 13 patients with acute respiratory failure given nifedipine, and Muramoto et al.[5] show no change in arterial PO_2 either at rest or during exercise in 9 subjects with chronic obstructive pulmonary disease given the agent. This lack of clinically significant desaturation after the administration of nifedipine in man might be explained on the basis of an increase in cardiac output and a decrease in arteriovenous oxygen content, as occurred in Muramoto's patients,[5] were it not for the fact that mixed venous PO_2 did not change in subjects studied by Simonneau et al.[4] Thus, the ventilation-perfusion relations that follow nifedipine administration may be unusually complex. Nevertheless, these agents offer promise in the treatment of patients with cor pulmonale in which low cardiac output is a factor limiting clinical well-being.

Acknowledgment

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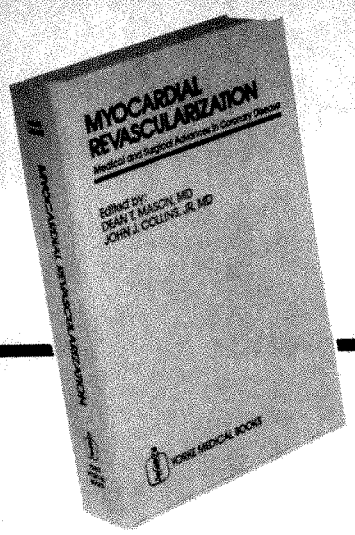

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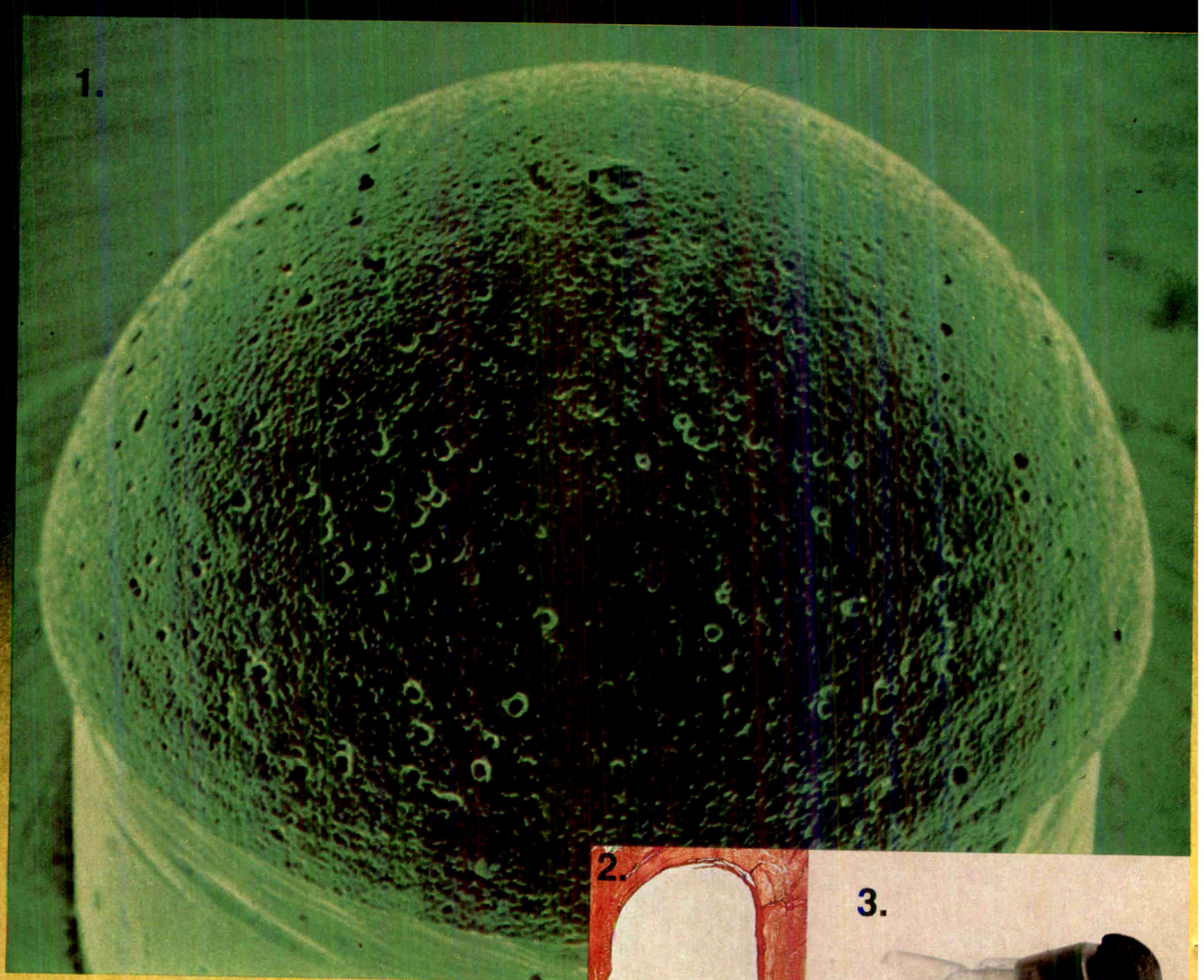

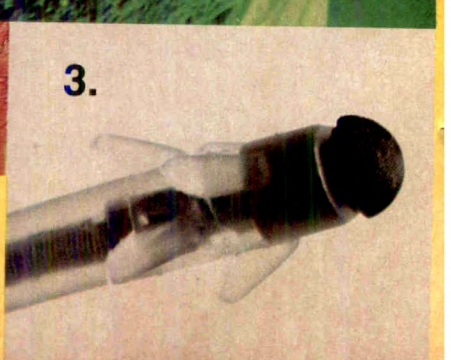

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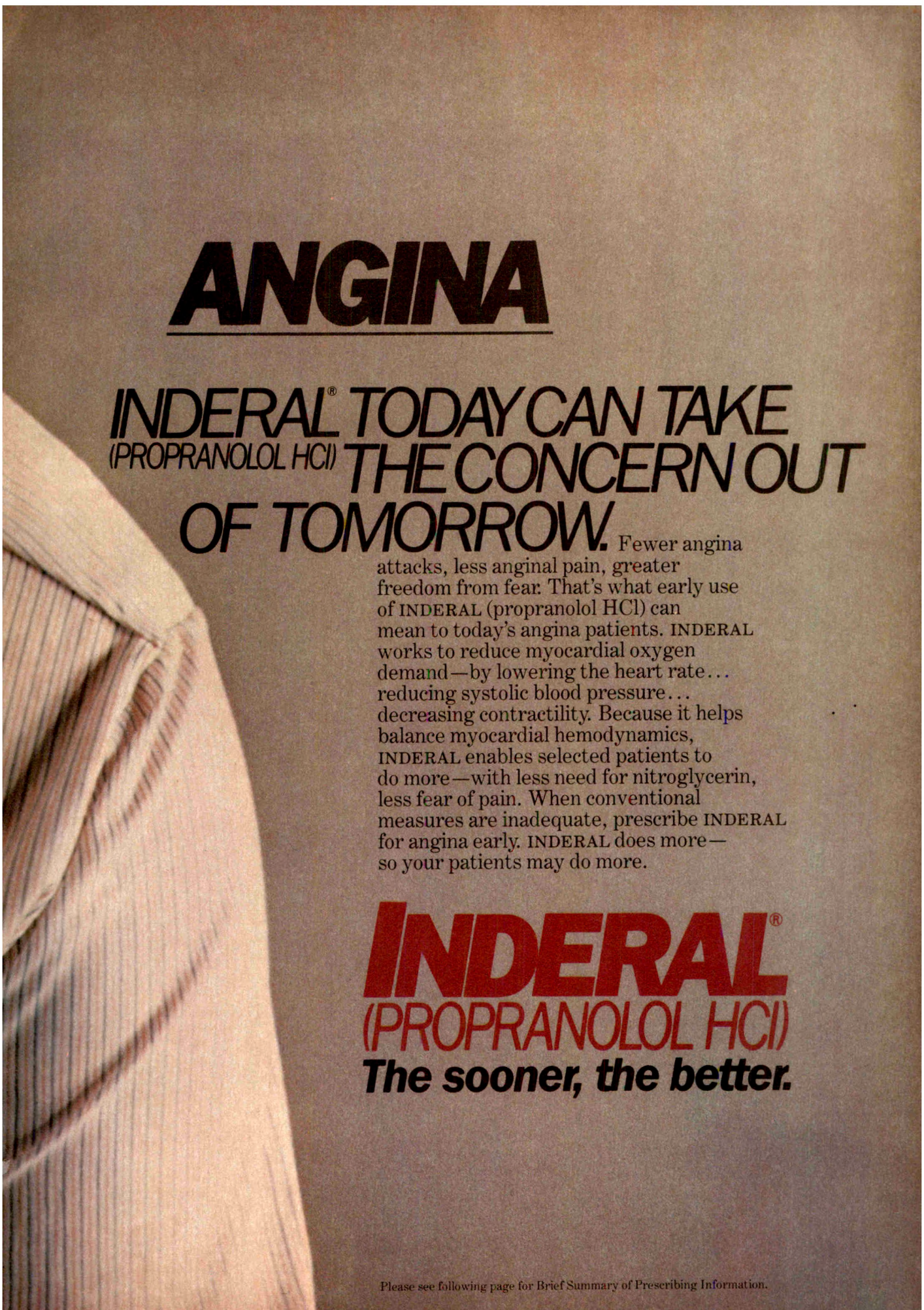
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IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

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PRECAUTIONS

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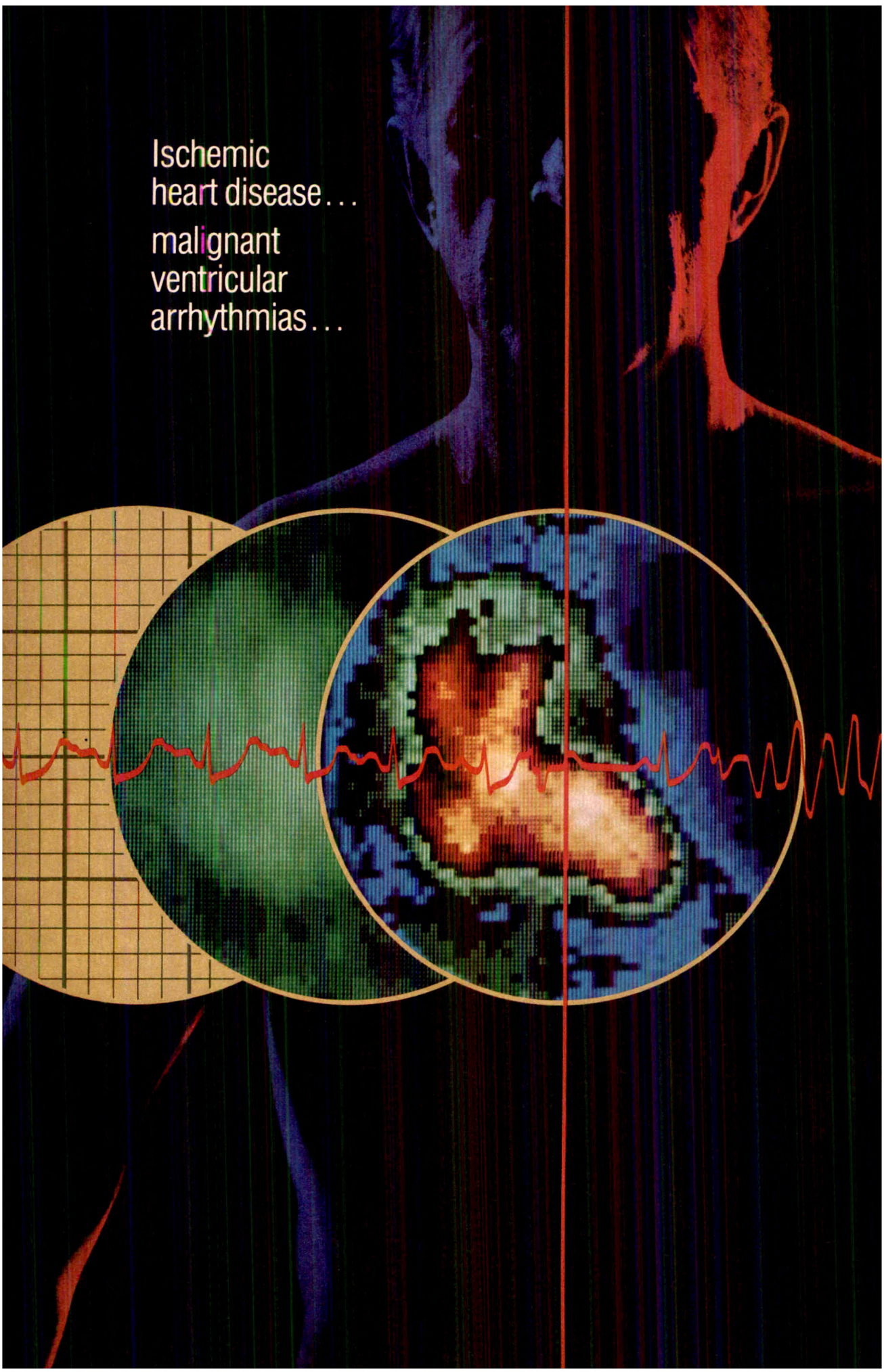
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CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.
WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.
2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered.
3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.
4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.
5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity.
7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.
8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.
PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.
Drug Interactions:

Drug	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
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Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.
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Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.
Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.
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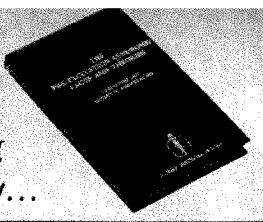

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC

Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC

Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—indeed, *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons why this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
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- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

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Effects of Angiographic Contrast Medium on Isolated Canine Coronary Arteries

HECTOR LARDANI, MD, GUSTAVO RINALDI, MD,* and HORACIO CINGOLANI, MD

In isolated canine coronary arteries previously contracted by high potassium concentration, angiographic contrast medium decreased active tension by 61 ± 2%. The relaxant effect was dose dependent and was not prevented by beta-blockade with d-l-propranolol (10^{-5} *M*). This effect was similar to that obtained with nitroglycerin (10^{-6} *M*), and further relaxation was evident when this vasodilator was administered after exposure to the contrast medium. When arteries were precontracted by alpha-receptor stimulation with norepinephrine (10^{-5} *M*) at normal potassium concentration, a maximal relaxation of 83 ± 6% was elicited after exposure to contrast medium. The relaxant effect could not be reproduced by a similar increase in osmolarity brought about by addition of sucrose. When arterial strips were processed by radioimmunoassay for dosage of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) after the relaxing action of the contrast medium occurred, a decrease in cAMP from 2.61 ± 0.86 to 0.63 ± 0.1 pmol/mg protein ($p < 0.05$) was observed, whereas no significant changes in cGMP were detected. These nucleotides do not appear to be involved in the relaxant effect of the dye in the same way as they are when relaxation is elicited by some other coronary vasodilators.

Selective coronary arteriography is being widely used for diagnostic purposes since early 1960.[1] However, despite some studies with contrast agents showing increased coronary flow after its injection[2,3] and preliminary reports on the effect of the contrast medium on isolated coronary arteries,[4,5] information about this subject is scarce.

Almost invariably, vasodilators are given during coronary arteriography to better define the caliber of the coronary arteries and collateral circulation and sometimes to study regional motion of the left ventricle. More recently provocative maneuvers such as cold pressor test,[6] hyperventilation,[7,8] and ergonovine administration[9] are being used to induce coronary spasm. These maneuvers are usually performed after a set of coronary arteriograms has been obtained for comparison. Obviously, in this "control" set the arteries are already exposed to the action of the contrast medium. It is then of interest to know the primary effect of the contrast agent on the coronary smooth muscle. A potent vasodilator effect induced by the contrast medium might perhaps mask the action of a vasodilator or attenuate a vasoconstrictor stimulus according to their respective intensity and mechanism of action.

The present investigation was therefore designed to study the effects of a largely used contrast agent on the coronary smooth muscle and to elucidate its possible mechanism of action.

Methods

Mongrel dogs of either sex were anesthetized with pentobarbital sodium (35 mg/kg) and killed by rapid excision of the heart. Sections of the circumflex or anterior descending branches of the left coronary artery or both were obtained and stripped of loose fat and connective tissue. Helical strips (2 to 3 mm wide, 0.2 to 0.3 mm thick, and 10 to 12 mm long) were cut and vertically mounted in a 15 ml muscle bath filled with Krebs-Henseleit (K-H) solution (Fig. 1). The composition of the solution was (in m*M*/liter): NaCl 118, KCl 5.32, NaH_2PO_4 1.54, $MgSO_4$ 1.19, $NaHCO_3$ 24.9, $CaCl_2$ 2.53, and EDTA 0.01; it was aerated with 5% carbon dioxide in oxygen (pH 7.42 ± 0.01) and maintained at 37° C. The inferior end of the strip was attached to a stationary rod and the other end was suspended from a Grass FTO3C force transducer whose output was driven to an oscillographic recorder. A resting tension of 2 g was obtained by stretching the strips, and they were allowed to equilibrate for 1 hour. A contracture was then elicited by replacing the standard K-H solution by another containing 35 m*M* potassium chloride and kept isoosmotic by equivalent reduction of the sodium chloride concentration.

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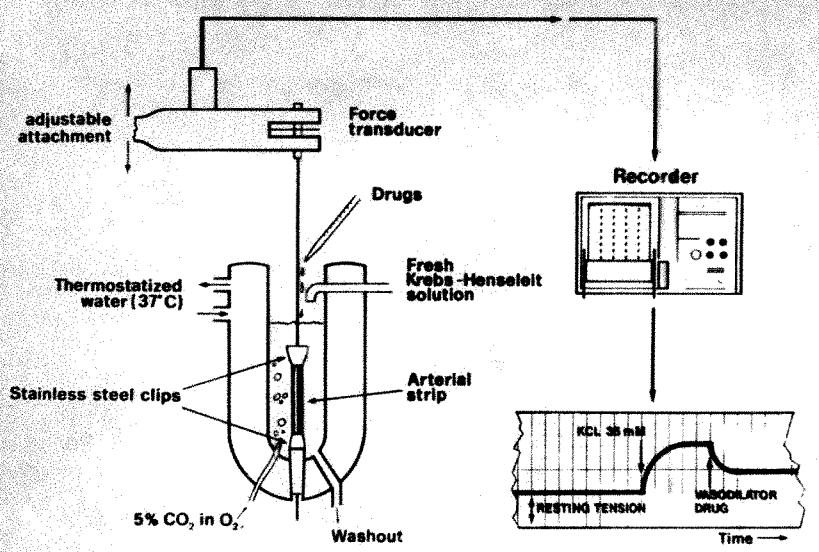

FIGURE 1. Experimental preparation used in the experiments. **Lower right,** schematic typical record.

After the preparation stabilized, the following groups of experiments were performed: *Group I* ($n = 33$): The time course of the contracture was studied for 1 hour and used as the control for the remaining mechanical studies.

Group II ($n = 15$): Cumulative dose-response curves for the contrast agent were performed, increasing its concentration to 33% vol/vol in 3% steps. Tension was allowed to stabilize after each dose, usually taking less than 5 minutes. Beta-blockade with d-l-propranolol 10^{-5} *M* was performed in 8 of these experiments before administration of the contrast agent. This dose of d-l-propranolol was shown to produce significant blockade in similar preparations.[10]

Group III ($n = 8$): Sucrose was added to the bath to obtain an increase in osmolarity comparable to that present when the 15% vol/vol dose of contrast medium was tested. This dose of dye was found to be most effective in the previous group.

Group IV ($n = 10$): After 30 minutes of beta-blockade with d-l-propranolol 10^{-5} *M*, contracture was elicited by the addition of norepinephrine 10^{-5} *M* to the normal K-H solution, and maintained for 5 minutes. After washing and returning to baseline, the entire procedure was repeated, and once contracture had stabilized the contrast agent was added to the bath in a 15% vol/vol dose and its effect studied.

After further washout, the ability to contract in response to the same norepinephrine challenge was assessed in 8 strips. *Group V* ($n = 22$): Nitroglycerin 10^{-6} *M* was added to the bath, and the relaxant effect was followed along time to compare it with the effect of the single dose of dye studied in group IV. The relaxant action of nitroglycerin was also studied in arterial strips previously exposed to a 15% vol/vol dose of contrast agent.

Group VI ($n = 31$): A single dose of 15% vol/vol of the contrast agent was added to the bath, and after the typical effect was recorded the strip was clamp-frozen, pulverized, and stored at −85°C. Dosage of adenosine 3′,5′-monophosphate (cAMP) and guanosine 3′,5′-monophosphate (cGMP) was performed with a modification of the radioimmunoassay method described by Steiner et al.[11,12] The protein content of the samples was calculated with the method of Lowry et

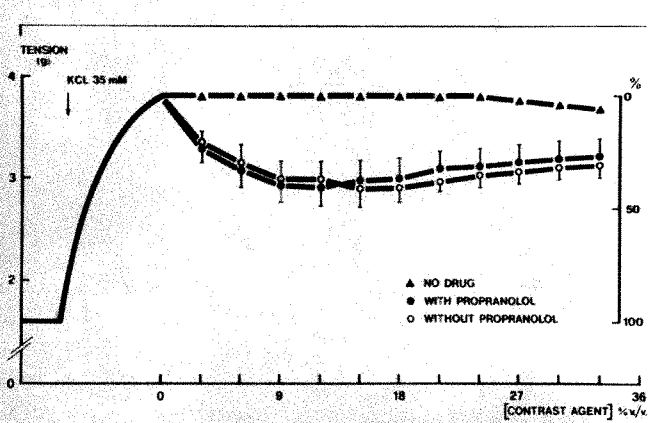

FIGURE 2. Relaxant effect of contrast agent on precontracted arterial strips, with and without beta-blockade. Time between doses was usually 5 minutes.

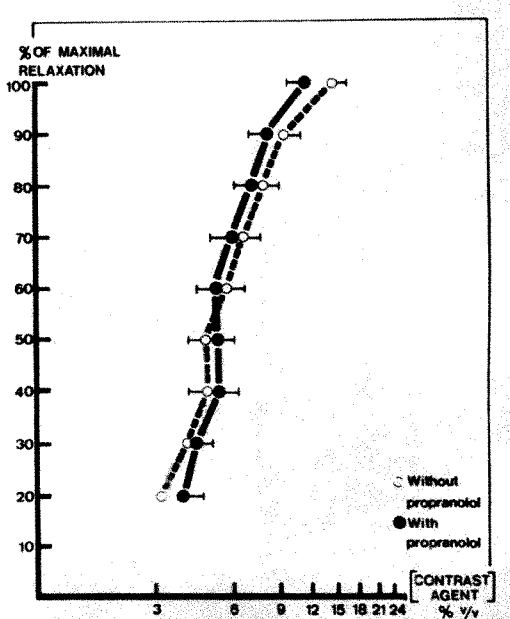

FIGURE 3. Dose-effect relation of the contrast agent, with and without beta-blockade. Drug concentration is on a logarithmic scale.

al.[13] and the cAMP and cGMP contents were expressed in picomoles per milligram of protein. Twenty-eight strips processed in the same way but without the addition of contrast medium were taken as the control in this group.

Drugs: The contrast medium was used as directed by the manufacturer for direct diagnostic use in man. Its composition (g/100 ml) was: sodium diatrizoate 10, meglumine diatrizoate 66, EDTA 0.01, and sodium biphosphate (Triyosom C, Gobbi Laboratories, Argentina) 0.012. This solution was warmed to 37° C before its addition to the bath. Nitroglycerin solution was obtained by diluting in K-H solution standard commercial tablets crushed to powder, and was freshly prepared each day.

The results were calculated as percentages of their own controls and expressed as mean ± standard error of the mean (SEM). Student's *t* test for unpaired observations and analysis of variance were used to analyze the results. Differences were considered statistically significant with $p < 0.05$.

Results

The K-H solution with 35 m*M* potassium chloride concentration elicited a contracture of 1.86 ± 0.2 g in the control experiments. The tension remained unaltered during the first 40 minutes, and a progressive but not statistically significant decrease was observed thereafter, reaching 95 ± 5% of control values at 1 hour (Fig. 2).

Cumulative doses of the contrast medium ranging from 3 to 15% vol/vol produced a dose-dependent relaxation in all the strips (Fig. 2). The maximal effect (41 ± 6%, $p < 0.05$) was obtained with the 15% vol/vol dose (Fig. 2 and 3). Higher concentrations of the dye had a smaller relaxant effect, but this action was still significant at the highest (33% vol/vol) dose employed (30 ± 5%, $p < 0.05$). Pretreatment of the strips with d-l-propranolol 10^{-5} *M* did not alter the previously described relaxant effect (Fig. 2 and 3). When the concentration of dye was elevated to 15% vol/vol in 1 step instead of following the progressive method described, a greater relaxation (61 ± 2%) was observed.

When an increase in osmolarity similar to the one produced by the 15% vol/vol dose of contrast medium was brought about by the addition of sucrose, a slight but significant relaxation (11 ± 2%) was observed. However, this effect was significantly smaller than the 61 ± 2% produced by the contrast medium at the same time (Fig. 4). This figure also shows the time course of the contrast agent action. Its effect, already evident a few seconds after its addition to the bath, was found significant at 20 seconds, and reached its maximal effect at 1 minute.

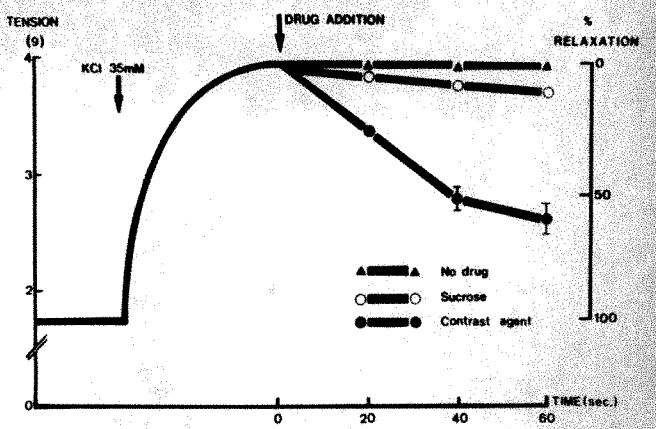

FIGURE 4. Comparative time course of the relaxant effects of the contrast agent and a similar increase in osmolarity brought about by the addition of sucrose to the bath.

In strips precontracted by alpha-receptor stimulation and at normal (5.32 m*M*) potassium chloride concentration the addition of contrast agent in a 15% vol/vol dose elicited a relaxation of 45 ± 5% after 20 seconds, reaching 83 ± 6% after 5 minutes (Table I). This relaxation was sustained, and the strips retained their ability to contract in response to a norepinephrine challenge after washing.

In another set of experiments the relaxing properties of the contrast medium were compared with those exhibited by a classic vasodilator such as nitroglycerin. A single dose of 10^{-6} *M* produced a maximal relaxation

TABLE I Relaxant Action of Angiographic Dye on Norepinephrine-Contracted Coronary Arterial Strips*

Experiment	With NE 10^{-5} *M*	Active Tension (mg)			
		Time After Addition of AD, 15% Vol/Vol			
		20 s	40 s	60 s	5 min
1	300	100	0	0	0
2	300	80	0	0	0
3	400	200	0	0	0
4	550	200	0	0	0
5	700	500	300	200	200
6	300	150	100	100	100
7	650	450	300	250	250
8	600	400	200	200	200
9	400	300	250	200	0
10	700	500	400	350	300
Mean	490	288†	155†	130†	75†
± SD	53	51	48	40	32

* Resting tension was 2,000 mg in all experiments. Beta-blockade with propranolol 10^{-5} *M* was performed 30 minutes before contraction.

† $p < 0.05$ with respect to control values.

AD = angiographic dye; NE = norepinephrine; SD = standard deviation.

of 61 ± 5%, whereas a single dose of the dye (15% vol/vol) produced a maximal effect of 62 ± 5%; the 2 values did not differ significantly (Fig. 5). This figure also shows the additive effect that was evident when nitroglycerin was administered after maximal relaxation with the contrast agent had already been obtained. This intervention produced a relaxation of 74 ± 5%, significantly greater than the one elicited by the contrast agent alone.

After maximal relaxation obtained by addition of the contrast agent, intracellular cAMP levels were significantly decreased from 2.61 ± 0.86 to 0.63 ± 0.1 pmol/mg protein. Cyclic GMP levels showed no significant variations under identical conditions, being 17.6 ± 2.9 pmol/mg protein in the control experiments and 20.9 ± 2.7 pmol/mg protein after the relaxing action of dye (Fig. 6).

Discussion

Little information is available on the primary effect of contrast medium on vasomotion of isolated coronary arteries. Our experiments demonstrated a potent relaxing effect, evident a few seconds after administration of the drug. When cumulative doses were used, the maximal relaxant effect was obtained with the 15% vol/vol dose (41 ± 6%). Higher concentrations of the drug showed a diminished relaxing action, being nevertheless significant at the highest dose tested (33% vol/vol). In another set of experiments in which a single dose of 15% vol/vol was used, the relaxing effect obtained was more marked (61 ± 5%). This difference in the intensity of relaxation might be related to a fade out in the effect of the initial doses when the cumulative method was employed.

A better estimation of the magnitude and chronology of this relaxing effect was attempted by performing experiments comparing the action of the contrast medium with that of a classic vasodilator (nitroglycerin). The intensity of relaxation was similar for the 15% vol/vol dose of contrast agent and for a dose of nitroglycerin large enough to mimic the concentration obtained by sublingual administration in clinical use. With respect to the time course of their actions, the contrast agent needed approximately twice the time required by nitroglycerin to reach the half maximal effect.

Experiments with beta-blockade with d-l-propranolol ruled out the hypothesis that the relaxing mechanism of the contrast medium was the stimulation of the beta receptor.

In experiments with sucrose at a concentration high enough to produce an increase in osmolarity similar to that present when the 15% vol/vol dose of dye was tested, a slight but significant relaxant effect was observed. However, because this action was significantly smaller than that observed with the contrast agent alone, hyperosmolarity by itself does not explain our findings.

To assess the relaxant effect of any pharmacologic agent on smooth muscle it must be previously contracted. Active tension development can be elicited by depolarization with high potassium solutions,[14,15] alpha-receptor stimulation,[16,17] or stimulation by other agents.[18–20] In our experiments the relaxant effect of the contrast agent was demonstrated in arteries precontracted either by high potassium solutions or by alpha-receptor stimulation with norepinephrine in solutions with normal potassium chloride concentration. These findings are interesting because the increase in the intracellular Ca^{2+} concentration, which is a prerequisite for active tension development, is probably achieved in two different ways by these two forms of stimulation. High potassium solutions (35 to 40 m*M*) cause an increased influx of Ca^{2+} through the cell membrane[14,15] whereas norepinephrine contraction appears more dependent on releasable intracellular

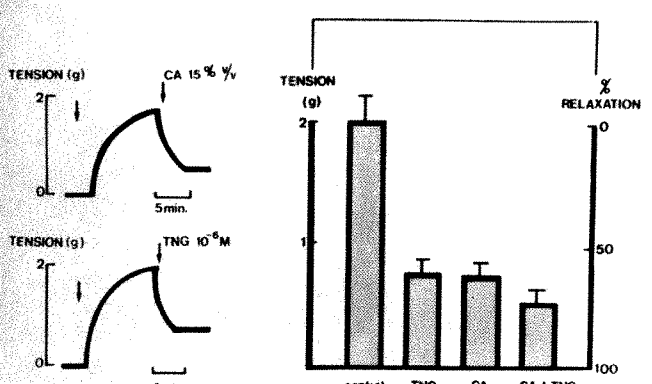

FIGURE 5. Top left, typical experiment showing the relaxant effect of nitroglycerin (TNG). **Bottom left,** typical experiment showing the relaxant effect of contrast agent (CA) and the additional relaxation obtained with the administration of nitroglycerin. **Left arrow** indicates potassium chloride concentration of 35 m*M*. **Right,** comparative effect of nitroglycerin, contrast agent and the addition of both.

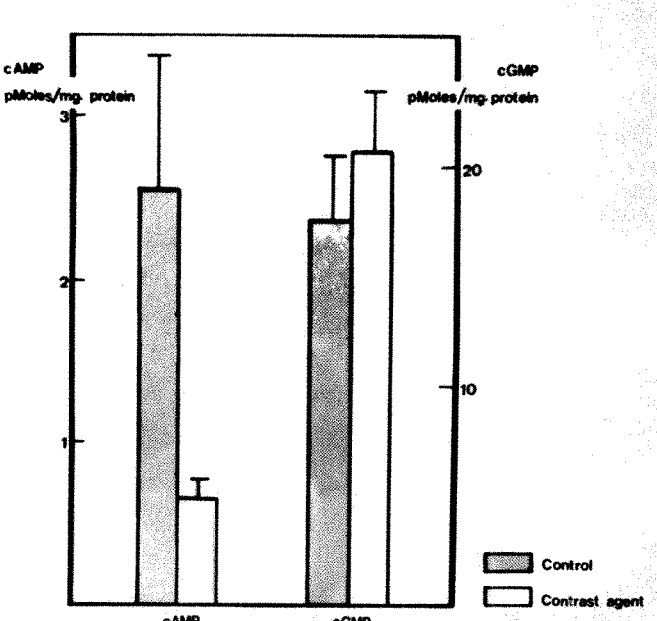

FIGURE 6. Intracellular levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) before and after the relaxant effect of contrast agent in a 15% vol/vol dose.

pools of Ca^{2+},[21,22] at least in its earlier phases.[23] However, in a recent report[24] the dog coronary artery was found to be more dependent on extracellular Ca^{2+} than other arteries.

The release of norepinephrine by exocytosis does not seem to play any role in our experimental conditions, because it has been found to be maximal when extracellular K^+ concentration is moderately high (10 to 15 m*M*) and minimal at K^+ concentrations above 20 m*M*.[25]

There is substantial evidence consistent with the hypothesis that cAMP can participate in intracellular processes that lead to coronary smooth muscle relaxation after the administration of beta agonists,[26,27] phosphodiesterase inhibitors,[28,29] adenosine,[30] prostacyclin,[31,32] and several other agents.[33] Böhme,[34] Schultz,[35] and co-workers suggested that cGMP might also be involved in mechanisms leading to a reduction in cytoplasmic Ca^{2+} and thus to smooth muscle relaxation. Available evidence about cGMP and relaxation reveal an interesting association between the intracellular increase of this nucleotide and the smooth muscle relaxation after nitroglycerin,[36] nitroprusside,[37] acetylcholine,[38] and carbachol.[36] Our results which show a significant decrease in cAMP levels in coronary arteries after the relaxation induced by the contrast medium seem to eliminate these nucleotides as the intracellular mediators. However, the preparation used in this study contains more than 1 cell type, and the possibility exists that the changes observed are reflecting changes occurring in nonmuscular cells. It is also possible that the cyclic nucleotides are compartmentalized within the cell and that changes in specific compartments undetected by total tissue measurements are important in the action of the compounds tested in our experiments. Nevertheless, the proposed role of the cyclic nucleotides in the control of the coronary vascular tone emerged from experimental preparations similar to the one we used.

Therefore, until additional evidence is obtained, our results suggest that at least in canine coronary arteries the contrast medium produces relaxation without significantly changing cGMP and despite a decrease in cAMP levels.

With the necessary caution in extrapolating basic research to the clinical setting, some practical information can be inferred from our data. When the effect of a drug on the coronary vascular bed is evaluated by means of angiography, the intrinsic relaxant effect of the angiographic dye should be taken into account. Also, provocative maneuvers frequently used to elicit coronary spasm should be interpreted cautiously, particularly when negative, because this might be attributed to the previous dilatation induced by the contrast agent.

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Digital Intravenous Ventriculography: Analysis and Validation of Wall Thickness Changes During Ischemia and Inotropic Stimulation in Dogs

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To assess regional ventricular wall thickening, we studied 8 open-chest dogs using digital intravenous ventriculography at a control stage, after subtotal and total coronary occlusion, and then after isoproterenol administration. In 3 dogs, 2 pairs of myocardial thickness crystals were implanted. Correlations of measures of wall thickness and percentage of wall thickening with crystal measures were excellent at the base ($r \geq 0.97$) and near the apex ($r \geq 0.97$). Four areas of the inferoapical wall muscle were measured: the base, mid-wall, distal wall, and apex. Four chamber dimensions were also examined: the long axis, base, mid-wall, and distal wall. End-diastolic thickness decreased with ischemia. At completion occlusion, it was $-24.6 \pm 6\%$ at the base, $-27.3 \pm 5\%$ at the mid-wall, $-27.1 \pm 5\%$ at the distal wall, and $-24.7 \pm 5\%$ at the apex. Percent thickening decreased with occlusion, although greater at the base and mid-wall than at the distal wall and apex. With isoproterenol, end-diastolic thickness increased only at the apex, with little change at the base, distal wall, and mid-wall. Percent thickening increased. In general, ischemia produced increases in end-diastolic hemichords with little change in the long axis. Isoproterenol reduced the hemichords, although the long axis did not change.

We conclude that digital intravenous ventriculograms can be used to assess changes in wall thickness with high degrees of accuracy. Asymmetric thickening occurred at rest, with ischemia and with inotropic stimulation, being greatest at the apex and least at the base.

Analysis of left ventricular wall thickness during the cardiac cycle has received considerable attention in both human and animal investigations.[1–14] Although the data vary with the model utilized, the technique applied, and the underlying hemodynamic condition, the normal ventricular free wall thickens from 20 to 50% during systole.[1–4,11] With acute coronary occlusion, end-diastolic wall thickness declines in large part because of changes in ventricle geometry and reductions in coronary blood flow and volume,[6] whereas systolic thinning occurs frequently.[3,4,7,9,12,13]

Application of contrast angiographic techniques to wall thickness analysis has generally been limited by difficulties in imaging the epicardial surface.[9,11] This problem may be due in part to radiographic and filming difficulties, in addition to mixing difficulties involved with direct chamber injections. Using a potentially simple noninvasive technique, digital intravenous ventriculography, we studied 8 open-chest animals during subtotal and total left circumflex coronary occlusion and then after the intravenous administration of isoproterenol. Wall thickness was measured in 4 locations at end-diastole and end-systole, as were 3 hemichords and a long axis. In 3 animals correlations between implanted wall thickness crystals and measured thickness were made in 2 locations at each intervention point.

The results demonstrate that data obtained from central intravenous injections allow the analysis of regional wall thickness and percent thickening with high degrees of accuracy at multiple intervention points. In addition, thickening appears to be progressively greater near the apex than at the base. This relation was preserved in the presence of both ischemia and inotropic stimulation.

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Methods

Animal Preparation

The experiments were conducted in 8 mongrel dogs anesthetized with morphine sulfate (5 mg/kg) and pentobarbital sodium (25 mg/kg). They were ventilated at a rate of 16/min using a Harvard positive-pressure respirator. Through a femoral vein an injection catheter (7 NIH) was placed in the inferior vena cava. Through a left thoracotomy an electro-

magnetic flow probe was placed around the left circumflex artery just proximal to a micromanometer arterial occluder. Another catheter was placed into the ascending aorta. In 5 dogs 2 ultrasonic crystals were placed in opposition on the endocardial surface of the left ventricular chamber distal to the occluder, and another pair were placed on a control region of the myocardium in the distribution of the anterior descending artery.

Ultrasonic crystals: To measure wall thickness in 3 dogs, 1 pair of ultrasonic crystals was placed into the myocardium at the base of the left ventricle, distal to the occluder, and 1 pair at the distal (inferior) wall. The subendocardial crystal was held at the top of a small Teflon® tube and advanced to a site close to the endocardium through a tunnel created by an 18 gauge needle. The epicardial crystal was sutured in place at the site where the ultrasonic transit time was shortest betwen the crystals. The crystals in both directions were positioned after the fluoroscopic position of the dog was established and subsequently used for ventricular imaging. The thickness crystals were then positioned, as well as possible, perpendicular to the fluoroscopic x-ray beam. They were positioned perpendicular to the long axis at both the base and the distal wall of the ventricle. These ultrasonic techniques were previously described and validated in this and other institutions.[4,15,16] The ultrasonic dimension gauge system continuously measures transit time between the piezoelectric crystals, and thereby monitors instantaneous left ventricular internal dimension or wall thickness. Along with an electrocardiographic limb lead, the hemodynamic data were continuously recorded on a multichannel (Gould 2400) direct writing recorder. Pressures were obtained from the aorta using a Statham P23db pressure transducer.

Hemodynamic Manipulations

After data from the control state were obtained, subtotal and total left circumflex occlusions were performed. Subtotal occlusions were defined as being present at the onset of mechanical changes (reduced shortening or thickening). At least 30 minutes were allowed to elapse between studies, permitting the animal to return to control state (defined by the pressure recordings as well as the ultrasonic information). This interval also allowed the effects of the contrast material to wane.[17] Finally, isoproterenol (Isuprel®) was administered (0.1 μg/kg/min) and a 4th series of data acquired.

Radiographic Techniques

A C-arm fluoroscopic unit (Philips, 6 inch cesium iodide image intensifier and a Vidicon television monitor) was located in the 10 to 15 left posterior oblique projection, and images obtained at 65 kV and 3 mA. Through the inferior vena cava, contrast medium was administered with a power injector at a rate of 30 ml/s for 1.0 second. In all studies meglumine sodium diatrizoate (Renografin®-76) was utilized.

Both fluoroscopic data and an electrocardiographic signal were stored in real-time on videotape (JVC high performance, 3/4 inch videotape recorder, CR6600U with a signal to noise ratio of 48 db). The data were then replayed and digitized using a commercially available general purpose medical computer and digitizer (MDS A^2, Ann Arbor, Michigan). Gated acquisitions were made at a rate of 60 fields a second (128 × 128 computer matrix).

Ventricular chamber dimensions and thickness measurements: End-diastole and end-systole were defined by an attenuation-time curve as the nadir and peak of the curve, respectively (Fig. 1). These curves were derived from a fixed left ventricular region-of-interest assigned in the 1st acquired frame (immediately after the R-wave trigger). The end-diastolic and end-systolic images were magnified and displayed on clear Kodak emulsion transparencies. Multiple grips were obtained and similarly magnified and displayed. During the study the distance for grid correction was directly measured (the animal's chest was left open in the pericardial cradle throughout the entire study). Measures of ventricular chamber dimensions and muscle thickness were traced (Fig. 2) and were obtained at end-diastole and end-systole after each intervention. Thus, end-diastolic chord length, volume, and muscle thickness could be manually obtained.

From the ultrasonic crystals, wall thickness at end-diastole was defined as occurring just prior to the upstroke of the aortic pressure recording and end-systole by the dichrotic notch.

At each point then the following chamber dimensions were obtained: (1) long axis, (2) base, (3) mid-wall, and (4) distal wall; and the following muscle thicknesses measured: (1) base, (2) apex, (3) distal wall, and (4) mid-wall. These locations were chosen by dividing the long axis equally by 4. The long axis was drawn from the apex to the juxtaposition of the mitral and aortic valves.

Cardiac output was derived from the heart rate × stroke volume. The latter was obtained from the single plane left ventriculogram and the formula of Kasser and Kennedy.[18] In our laboratory the correlation for this calculation and triplicate thermodilution estimates of cardiac output were tested and found to be excellent (n = 24, r = 0.87). In the 3 dogs with implanted thickness crystals, base and distal wall thicknesses were compared with the angiographic values.

Role of contrast medium: Intravenous administration of contrast material is a requisite for imaging the cardiovascular system with computerized tomography and digital subtraction techniques. In addition to defining anatomy, these modalities have been used to derive physiologic data such as (1) calculation of cardiac output, (2) left ventricular wall thickening, and (3) segmental contraction. An important consideration in the physiologic interpretations of these techniques is the potential hemodynamic alterations caused by the intravenous administration of the contrast material. In a previously completed study,[17] we found that the amount of contrast material utilized in the present study will not alter cardiac hemodynamics if sufficient time elapses between studies (15 to 20 minutes).

Digital Image Manipulation

Acquisition: The videotaped fluoroscopic data were digitized off-line onto an image processing computer (MDS A^2). The information was digitized at a rate of 30 frames/s, with

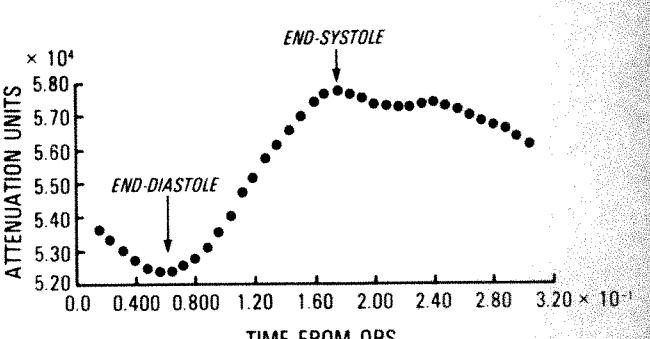

FIGURE 1. Left ventricular time-attenuation curve derived from a fixed, manually assigned left ventricular region-of-interest assigned in the first frame after the peak of the R wave. End-diastole was chosen as the early nadir of the curve and end-systole as the later apex.

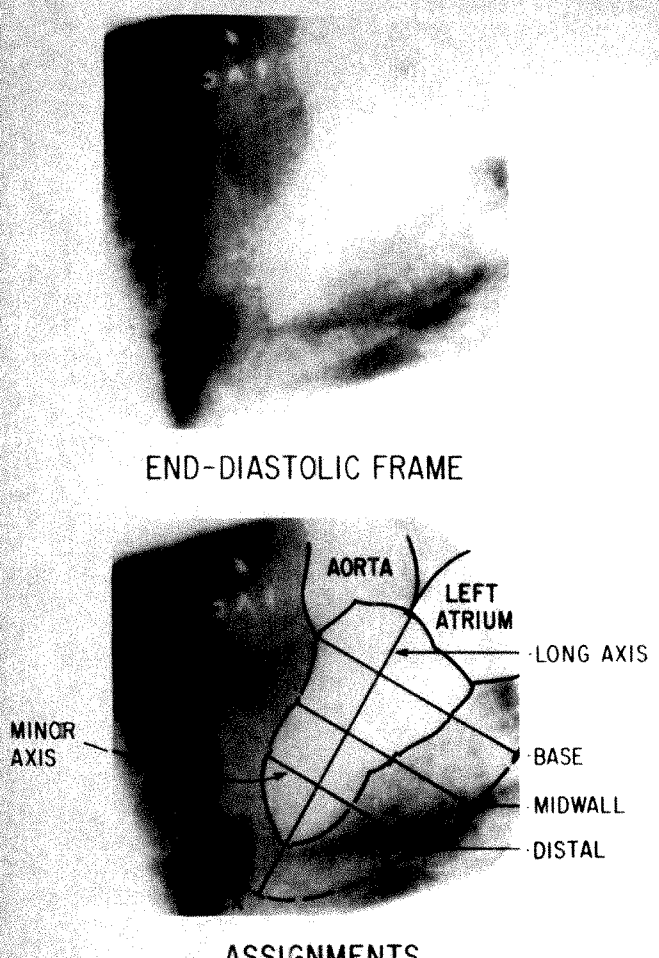

FIGURE 2. Measurements of ventricular chamber dimensions on the digital images and wall thickness. No filtering or subtraction was performed. See text for discussion of the measurements.

2 complete interlaced video fields per frame. The R wave of the electrocardiogram was detected by a physiologic trigger (Picker Cardiac Module) and this signal was used by the computer to initiate acquisition of a single heart beat. Digital acquisition was controlled by the operator to coincide with peak opacification of the left ventricle. Data were recorded in a 128 × 128 matrix with 256 levels of gray. This image matrix yielded a spatial resolution of 1.19 mm/pixel using the 15.24 cm (6 inch) image intensifier.

Image filtering: Temporal frequency filtering was performed on the data as the initial step in improving image quality. Dynamic studies of the cardiovascular system are particularly well suited to this technique. Because the motion of the heart is relatively smooth and undulatory, the individual time-varying frames comprising the study should also be expected to change smoothly and continuously. Stepwise changes occurring from 1 frame to the next are likely attributable to random statistical noise. Rapid changes are characterized by high temporal frequencies; therefore, by frequency filtering in the time domain (temporal frequency filtering), significant improvements in image quality can be obtained because a large amount of medium and high frequency noise can be eliminated while at the same time retaining virtually all of the important low frequencies containing image data. In the present study temporal frequency filtering was performed using a truncated convolution operator to minimize processing time.

Contrast enhancement: Although the data were acquired with 256 levels of gray, not all of these levels corresponded to intensities of interest. For example, regions over the lung fields have minimal x-ray attenuation or maximal x-ray transmission. Because these values were not of interest in the present study, they were displayed with lower gray scale values, and the attenuation values corresponding to the ventricle and its surrounding structures were spread out over the larger portion of the gray scale. This technique for density "windowing" is analogous to the technique used in computerized tomography, wherein only those structures having attenuation values within the operator-selected window are displayed. Both digital radiographic images and computerized tomographic images displayed in this manner allow for discrimination of significantly more subtle degrees of attenuation difference than would be apparent if the data were displayed without windowing.

Statistics: All results are given as the group mean ±1 standard deviation. Differences were tested with a repeated measures analysis of variance for overall significance and the paired t test for individual mean values at various time intervals.[19] Linear correlations were performed using a least-squares linear fit.

Results

Hemodynamics: Cardiac output was 180 ± 60 ml/kg at rest. Stroke volume was 1.76 ± 0.41 ml/kg, heart rate 114 ± 9.4 beats/min, and mean arterial pressure 126 ± 8.5 mm Hg.

With subtotal occlusion induced by a mean reduction in coronary flow of 62.6 ± 4% ($p < 0.01$), cardiac output (170.5 ± 26 ml/kg) declined insignificantly. Arterial pressure declined from the control value (119.0 ± 1.3 versus 126 ± 8.5 mm Hg, $p < 0.05$). With total left circumflex occlusion, mean arterial pressure declined even further (115 ± 12.3 mm Hg, $p < 0.01$ versus control), with a continued although slight decline in cardiac output (169.1 ± 24.9 ml/kg, $p < 0.05$ versus control). Heart rate increased slightly over control values (122 ± 7.9 beats/min, $p < 0.05$), and stroke volume declined (1.37 ± 0.39 ml/kg, $p < 0.05$).

With isoproterenol administration, coronary flow increased (mean increase of 32.8 ± 29.1%, $p < 0.005$ versus control) and mean arterial pressure declined (107 ± 11.3 versus 126.0 ± 8.5 mm Hg at the control data point, $p < 0.01$). Both stroke volume (2.4 ± 0.4 ml/kg, $p < 0.01$) and heart rate (133 ± 11.9 beats/min, $p < 0.01$) were greater than control values.

Thickness correlation data: In 3 dogs, 2 pairs of thickness crystals (1 at the base and 1 at the distal wall) allowed comparisons to be made between the ultrasonic and angiographic methods. Data were obtained at the control state and at all 3 intervention points (subtotal occlusion, total occlusion, and isoproterenol infusion).

The correlation between end-diastolic thickness and percent thickening for the base and distal wall regions was excellent ($r \geq 0.97$) (Fig. 3 and 4). Note that the slope of the thickness measurement at the base is less than the slope from the data at the distal wall. This may be a statistical error, but more likely represents dif-

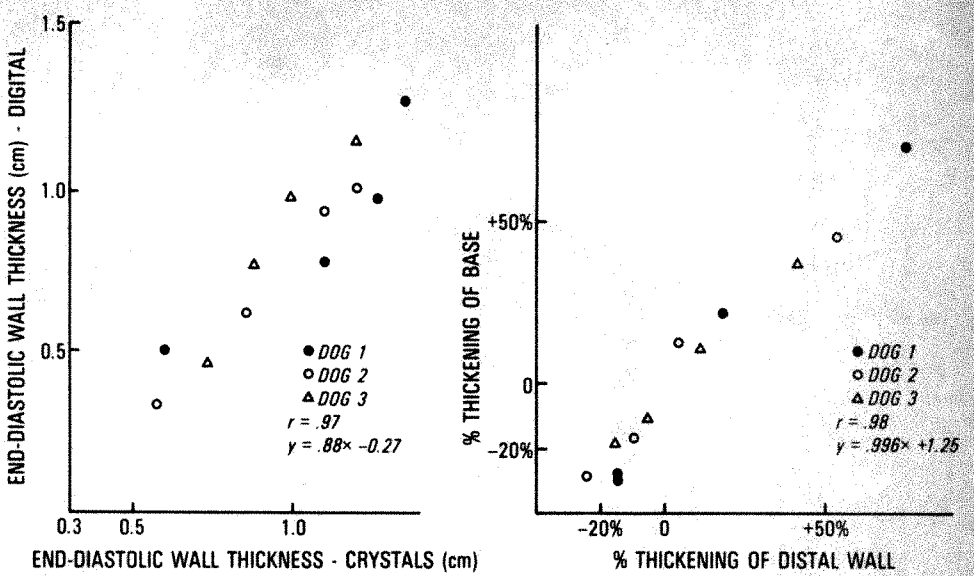

FIGURE 3. Correlations of the percent thickening and end-diastolic wall thickness at the base are given for the digital radiographic (**ordinate**) and sonomicrometer (**abscissa**) techniques.

ficulties with placement of 2 pairs of perfectly parallel sonomicrometers.

End-diastolic thickness and systolic thickening (Fig. 5 and 6): At control level, thickness varied from a mean value of 9.7 ± 1.8 mm at the apex ($p < 0.01$) to 13.4 ± 1.4 mm at the base, 15.6 ± 2.1 mm at the mid-wall, and 14.4 ± 2.1 mm at the distal wall. Mean thickness (average of all 4 locations) was 13.4 ± 2.2 mm. Percent thickening increased as the apex was approached, and was 22.2 ± 13% at the base, 27.6 ± 12.1% at the mid-wall, 43.8 ± 13.0% at the distal wall ($p < 0.05$ versus mid-wall and base), and 61.9 ± 37.3% at the apex ($p < 0.01$ versus base and mid-wall, $p < 0.05$ versus distal wall). The mean percent thickening (average of all 4 locations) was 38.9 ± 17.9%.

Subtotal occlusion induced thinning of the muscle at end-diastole (mean reduction in thickness of 8.4 ± 3.1% versus control, $p < 0.05$). The decline in thickness was 1.5 ± 0.4 mm at the mid-wall, 1.3 + 0.5 mm at the distal wall, and 0.4 ± 0.7 mm at the apex. Percent thickening declined to 5.5 ± 14.7% at the base, 10.4 ± 13.6% at the mid-wall, 29.1 ± 18.3% at the distal wall ($p < 0.05$ versus mid-wall and base) and 68.0 ± 53.0% at the apex ($p < 0.01$ versus mid-wall and base, $p < 0.05$ versus distal wall). Thickening thus appeared to be preserved distally while lost proximally.

With total circumflex occlusion, thinning of the muscle at end-diastole was greater than that at subtotal occlusion. Mean thickness (average of 4 regions) was 9.8 ± 1.8 mm ($p < 0.05$ versus subtotal occlusion value of 12.1 ± 21 mm and $p < 0.01$ versus the control value of 13.3 ± 2.5 mm). The reduction in end-diastolic thickness was similar in all 4 regions (25 ± 6% reduction at the base, 27 ± 4% reduction at the mid-wall, 27 ± 5%

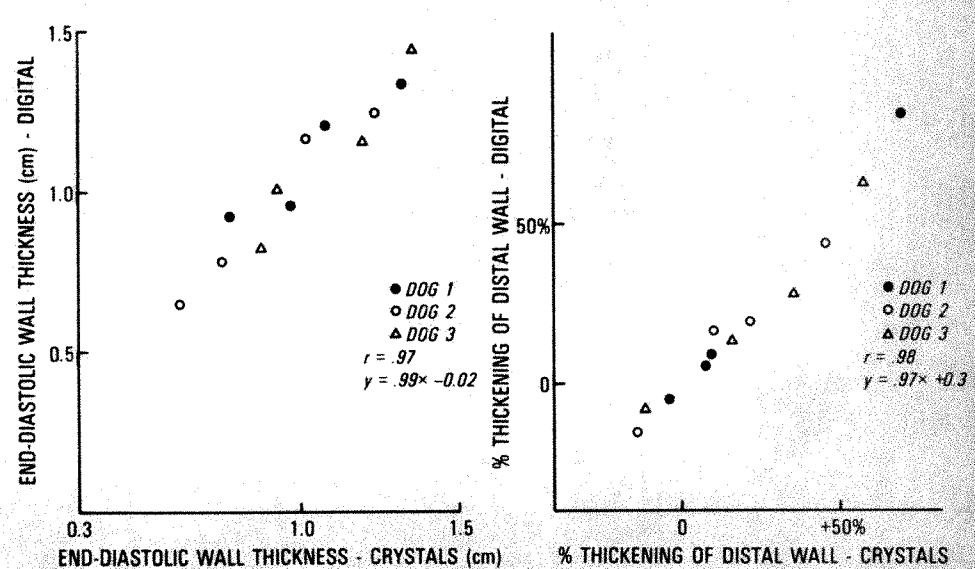

FIGURE 4. Similar to Figure 3 in design. Distal wall thickness correlation data are plotted in the same format as in Figure 3.

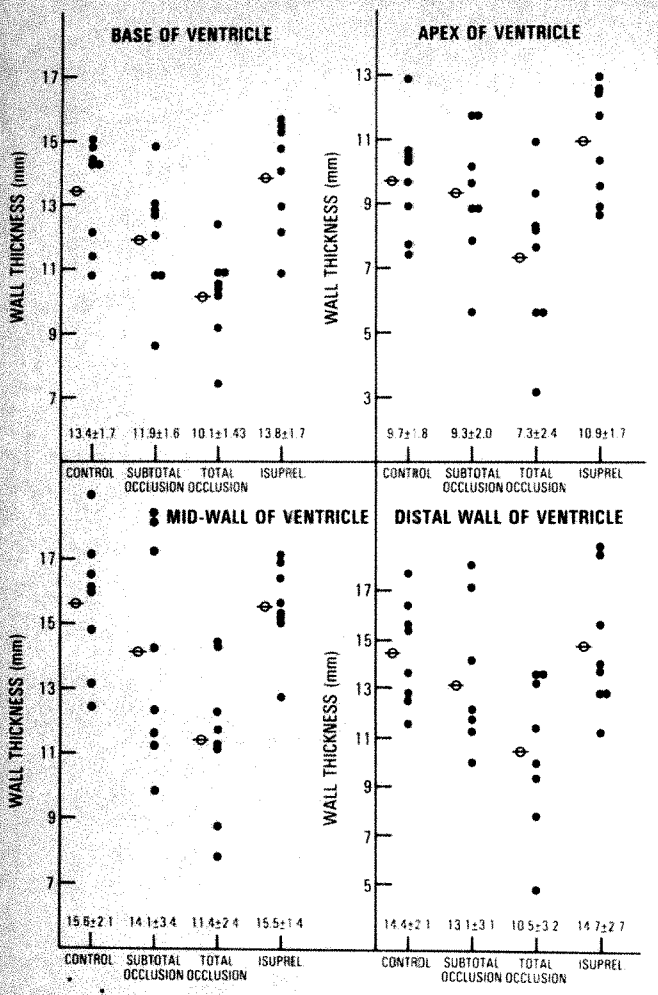

FIGURE 5. End-diastolic wall thickness at each intervention point and at each ventricular region are given. Interventions include subtotal and total coronary occlusion and isoproterenol (ISUPREL).

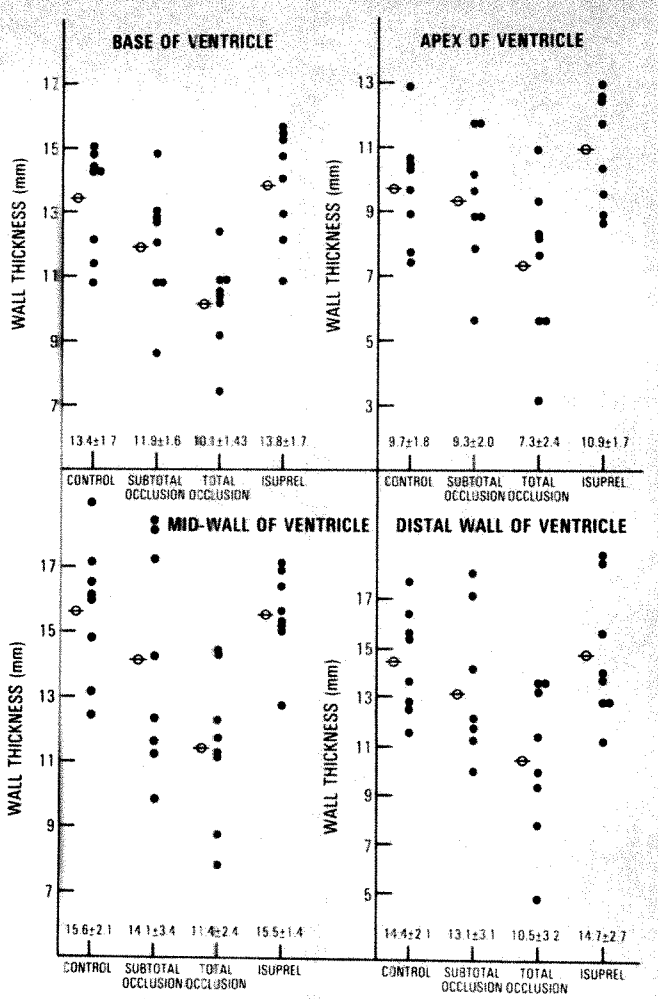

FIGURE 6. Percent wall thickening is given at each region during each intervention in format similar to that in Figure 5.

reduction at the distal wall, and 25 ± 3% at the apex), although the absolute reduction varied with the region analyzed (−3.3 ± 0.7 mm at the base, −4.2 ± 1.1 mm at the mid-wall, −3.9 ± 0.9 mm at the distal wall, and −2.4 ± 0.5 mm at the apex).

Percent thickening followed a similar pattern as seen at the subtotal occlusion intervention point. Thickening tended to be greater distally than near the base. The mean percent thickening was 6.3 ± 10% (average of all 4 regions) and varied from 2.1 ± 27.4% at the distal wall ($p < 0.05$ versus base and mid-wall) and 26.5 ± 30% at the apex ($p < 0.01$ versus base and mid-wall, $p < 0.05$ versus distal wall).

With isoproterenol, the progressive increase in percentage of thickening towards the apex continued to be observed. The mean percent thickening of all 4 regions was 76.8 ± 40.5%, and progressed from 49.1 ± 20.3% at the base, to 60 ± 20.9% at the mid-wall, to 60.9 ± 17.2% at the distal wall, and to 137 ± 35.8% ($p < 0.01$) at the apex. End-diastolic thickness averaged 13.7 ± 2.0 cm (not significantly different from the control value of 13.3 ± 2.5 cm) and was 13.8 ± 1.7 cm at the base, 15.5 ± 1.4 cm at the mid-wall, 14.7 ± 2.7 at the distal wall, and 10.9 ± 1.7 at the apex ($p < 0.05$ versus control value of 9.7 ± 1.8 cm).

Chamber dimensions and systolic shortening (Fig. 7 and 8): In the control state, the long axis was 59.0 ± 8.4 mm compared with 29.0 ± 7.2 mm at the base, 28.0 ± 7.7 mm at the mid-wall, and 23.3 ± 5.4 mm at the distal wall. The ratio of the mid-wall dimension to the long axis was 0.47 ± 0.06. With subtotal and total coronary occlusion, the long axis increased (60.0 ± 9.4 mm and 64.1 ± 14.5 mm, respectively; only the latter different from control, $p < 0.05$). The base widened (from 29.0 ± 72 to 32.3 ± 6.1 to 37.9 ± 8.7 mm, $p < 0.01$ for total occlusion versus control, and $p < 0.05$ versus subtotal occlusion) as did the mid-wall dimension (28.0 ± 7.7, to 30.9 ± 5.3, to 39.5 ± 10.8 mm, $p < 0.01$ for occlusion versus control and subtotal occlusion) and the distal wall dimension (23.3 ± 5.4, to 25.8 ± 4.7, to 33.7 ± 9.5 mm, total occlusion $p < 0.01$ versus control and $p < 0.05$ versus subtotal occlusion). The ratio of the mid-wall dimension to long axis increased (0.47 ± 0.06 at control, to 0.48 ± 0.07 at subtotal occlusion, to 0.62 ± 0.08 at total occlusion; the latter $p < 0.01$ versus control and subtotal occlusion).

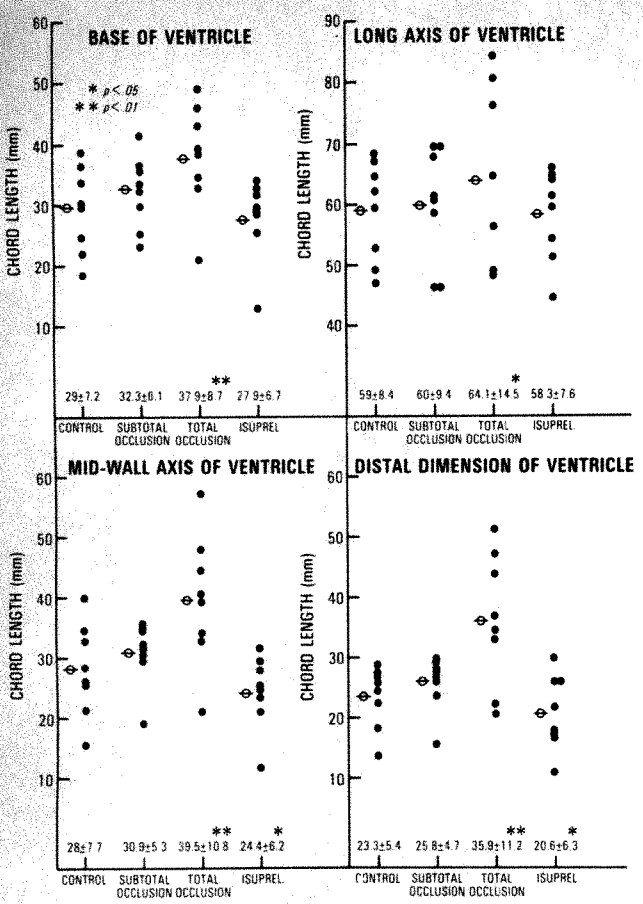

FIGURE 7. Chamber dimensions (long axis and 3 minor chords) are given at each region during each intervention. Format similar to that in Figure 5.

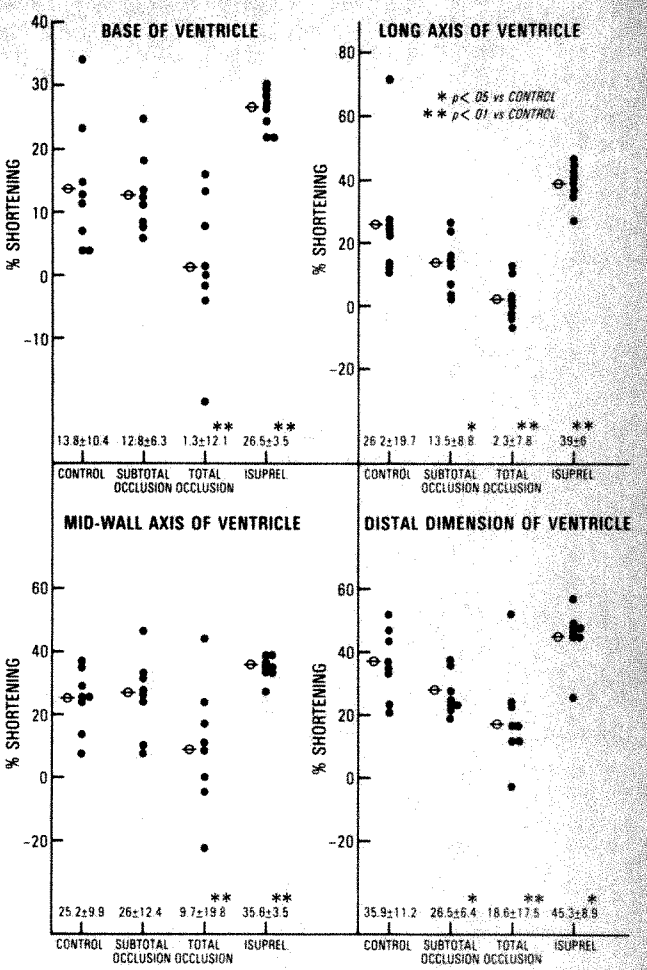

FIGURE 8. Percent dimension (internal chamber dimension) is given at each region during each intervention. Format similar to that in Figure 5.

The percent shortening (%) at the control state was 13.8 ± 10.4 at the base, 25.2 ± 9.9 at the mid-wall, 35.9 ± 11.2 at the distal wall, and 26.2 ± 19.7 at the apex. With subtotal occlusion, few changes in chamber shortening occurred. With total occlusion, all regions shortened less (1.3 ± 12.1% at the base, $p < 0.01$ versus control; 9.7 ± 19.8% at the mid-wall, $p < 0.01$ versus control; 18.6 ± 17.5% at the distal wall, $p < 0.01$ versus control; and 2.3 ± 7.8% at the apex, $p < 0.01$ versus control). Note that shortening was greater at the distal wall than at the base, and that this finding persisted with ischemic interventions.

Isoproterenol produced increases in shortening, again with the base shortening less than the distal wall (26.5 ± 3.1% at the base, 35.6 ± 3.5% at the mid-wall, 45.3 ± 8.9% at the distal wall, and 39 ± 6% at the long axis; all $p < 0.01$ versus control values). Neither the long axis nor the base dimension was different from the respective control values (58.3 ± 7.6 versus 59.0 ± 8.4 mm and 27.9 ± 6.7 versus 39.0 ± 72 mm). However, the mid-wall and distal wall dimensions were significantly smaller (24.4 ± 6.2 versus 30.9 ± 5.3 mm, $p < 0.05$, respectively). The ratio of the mid-wall dimension to the long axis decreased (0.41 ± 0.008, $p < 0.05$ versus control and subtotal occlusion and $p < 0.01$ versus total occlusion).

Discussion

Methodologic considerations: As in previous studies, we found that myocardial thickening in the basal state varies from 20 to 50%. Previous studies using contrast ventriculography to identify the myocardial wall have proved difficult, particularly when left ventricular hypertrophy was present.[11] Our data in open-chest dogs suggest that digital ventriculography may be a feasible technique for estimating wall thickness and percent thickening. Unlike in previous studies,[10,11] contrast medium was injected into the inferior vena cava, thus permitting excellent mixing with the blood pool. Additionally, lower transmission x-ray energy maximized attenuation differences between the contrast-containing blood in the chamber, the myocardial muscle (with less blood), and the lung. However, our study involved open-chest animals, with images performed at held inhalation. Moreover, none of the animals had left ventricular hypertrophy, although with isoproterenol infusion the end-systolic thickness approximated this condition. It might be pointed out that the isoproterenol correlation data appeared identical to the control and ischemia data.

Rotation during systole was neither measured nor corrected for; nonetheless, in this projection it did not appear to influence the results or correlations. Importantly, the inferoposterior wall was chosen because it did not overlap with the right ventricular chamber and wall in this projection. The anterolateral wall (in the traditional more shallow right anterior oblique view) may conceivably be more prone to rotational distortion. Alteration of the geometric configuration of the muscle at end-systole in the right anterior oblique view might result in alterations in the anatomic configuration of the ventricular muscle tangential to the x-ray beam, and could produce inaccurate overestimations of wall thickness and percent thickening. In 4 dogs, tantalum markers were sutured to the apex (apical dimple) and to the area near the aortic and mitral valve (appendage). The rotation of the line connecting these 2 points was less than 10%. Nonetheless, rotation out of the unidimensional plane could not be corrected for and must remain a significant problem and limitation of the method.

Effect of ischemia on systolic ventricular wall thickening: In the "basal" (open-chest, morphine-pentobarbital anesthesia, held inhalation) state, systolic thickening appeared greater towards the apex and less towards the base. With ischemia (total and subtotal occlusion), these relations were maintained. It is difficult to know whether the distal wall and apex received more collateral flow, thus permitting contraction. It did appear that the decline in thickening was similar in all regions, but the apex and distal wall started at greater absolute percent thickening. Isoproterenol provoked increases in percent thickening in a pattern similar to the rest and ischemia data. Of note was the fact that end-diastolic thickness was only greater at the apex after flow was increased. Ischemia produced gradual decreases in end-diastolic thickness. The latter findings are in all likelihood due to the reduction in coronary flow and the change in ventricular chamber geometry. With ischemia (particularly in total occlusion), the ventricular chamber assumes a more spherical configuration; that is, the ratio of the mid-wall dimension/long axis more closely approaches unity. This might result in end-diastolic thinning. Nonetheless, Gaasch and Bernard[6] showed the thinning effects of ischemia on the end-diastolic muscle dimension. They also demonstrated that with reperfusion hyperemia and coronary papaverine and nitroglycerin injections, increases in coronary flow produced increases in end-diastolic wall thickness. The flow changes in their experiments were substantially greater than those in our studies. We were unable to accurately assess ischemic reperfusion because of the limited number of contrast injections that could be performed without producing hemodynamic changes, and isoproterenol only increased flow by approximately 30%.

Similar to other investigators using a variety of other techniques,[3,4,6-9] we found that ischemia reduced percent thickening and end-diastolic thickness. Occasionally, end-systolic thinning occurred, particularly at the base and mid-wall. Chamber dimensions increased with ischemia, and percent shortening declined. These changes corresponded to an increase in end-diastolic volume and a decline in cardiac output and stroke volume.

Implications: We conclude that digital intravenous ventriculography is a useful technique for the evaluation of myocardial wall thickness and chamber geometry in dogs. Measurements of wall dimensions correlate well with standard sonomicrometer measures, and changes in 1 technique agree well with changes in the other. Whether this technique is feasible in man, when the chest is closed, the anteroposterior diameter is greater, and the administered contrast medium doses are lower, will require extensive further investigation.

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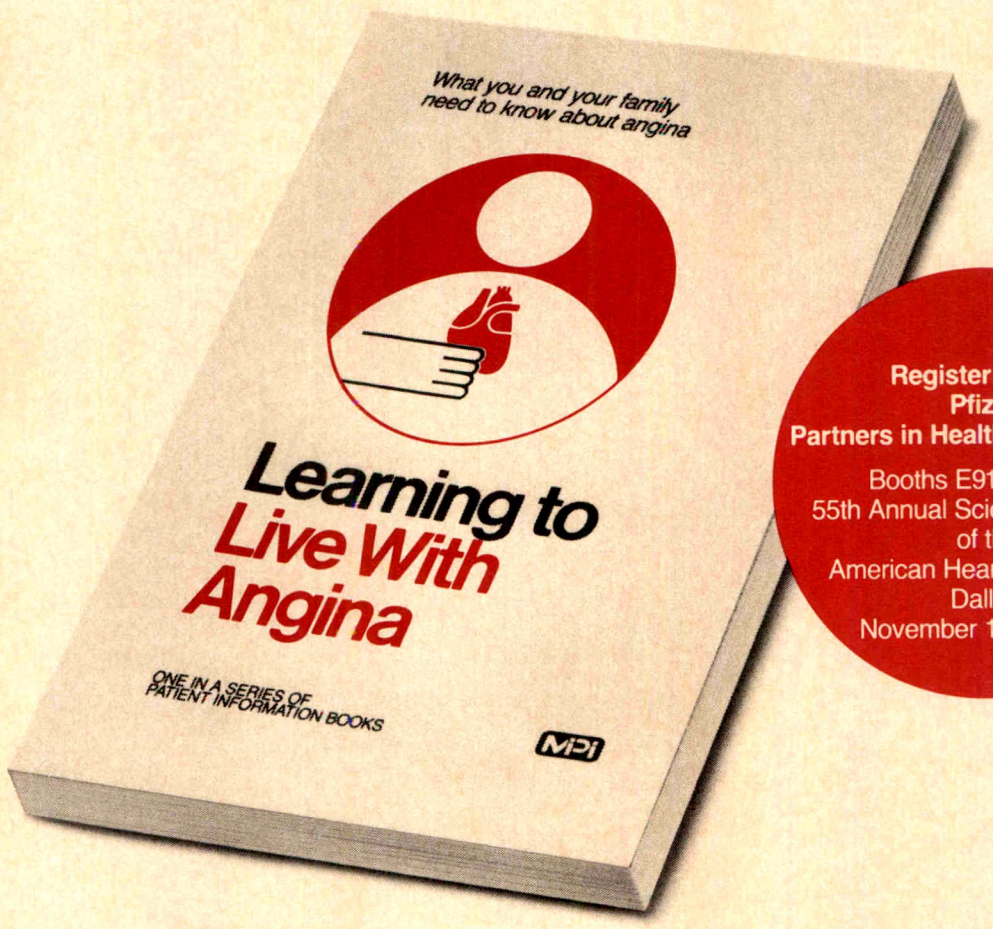

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TRIDIL® (nitroglycerin) SYSTEM

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TRIDIL® (nitroglycerin)

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NOT FOR DIRECT INTRAVENOUS INJECTION. TRIDIL® MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION (SEE DOSAGE AND ADMINISTRATION SECTION OF FULL PRESCRIBING INFORMATION). THE ADMINISTRATION SET USED FOR INFUSION WILL AFFECT THE AMOUNT OF TRIDIL DELIVERED TO THE PATIENT. (SEE WARNINGS, AND DOSAGE AND ADMINISTRATION SECTIONS.)

CAUTION

SEVERAL PREPARATIONS OF NITROGLYCERIN FOR INJECTION ARE AVAILABLE. THEY DIFFER IN CONCENTRATION AND/OR VOLUME PER VIAL. WHEN SWITCHING FROM ONE PRODUCT TO ANOTHER ATTENTION MUST BE PAID TO THE DILUTION AND DOSAGE AND ADMINISTRATION INSTRUCTIONS.

CONTRAINDICATIONS

TRIDIL should not be administered to individuals with:

1. A known hypersensitivity to nitroglycerin or a known idiosyncratic reaction to organic nitrates.
2. Hypotension or uncorrected hypovolemia, as the use of TRIDIL in such states could produce severe hypotension or shock.
3. Increased intracranial pressure (e.g., head trauma or cerebral hemorrhage).
4. Constrictive pericarditis and pericardial tamponade.

WARNINGS

1. Nitroglycerin readily migrates into many plastics. To avoid absorption of nitroglycerin into plastic parenteral solution containers, the dilution and storage of TRIDIL for intravenous infusion should be made only in *glass* parenteral solution bottles.
2. Some filters absorb nitroglycerin; they should be avoided.
3. Forty to 80% of the total amount of nitroglycerin in the final diluted solution for infusion is absorbed by the polyvinylchloride (PVC) tubing of the intravenous administration sets currently in general use. The higher rates of absorption occur when flow rates are low, nitroglycerin concentrations are high, and the administration set is long. Although the rate of loss is highest during the early phase of infusion (when flow rates are lowest) the loss is neither constant nor self-limiting; consequently no simple calculation or correction can be performed to convert the theoretical infusion rate (based on the concentration of the infusion solution) to the actual delivery rate.

Because of this problem, American Critical Care has developed TRIDILSET,™ an administration set in which loss of TRIDIL is minimal (less than 1%). TRIDILSET (or a similar administration set) is recommended for infusions of TRIDIL.

DOSING INSTRUCTIONS MUST BE FOLLOWED WITH CARE. IT SHOULD BE NOTED THAT WHEN TRIDILSET IS USED, THE CALCULATED DOSE WILL BE DELIVERED TO THE PATIENT BECAUSE THE LOSS OF TRIDIL DUE TO ABSORPTION IN STANDARD PVC TUBING WILL BE KEPT TO A MINIMUM. NOTE THAT THE DOSAGES COMMONLY USED IN PUBLISHED STUDIES UTILIZED GENERAL-USE PVC ADMINISTRATION SETS AND RECOMMENDED DOSES BASED ON THIS EXPERIENCE ARE TOO HIGH WHEN TRIDILSET IS USED.

PRECAUTIONS

TRIDIL (nitroglycerin) should be used with caution in patients with severe liver or renal disease.

Excessive hypotension, especially for prolonged periods of time, must be avoided because of possible deleterious effects on the brain, heart, liver, and kidney from poor perfusion and the attendant risk of ischemia, thrombosis, and altered function of these organs. Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Patients with normal or low pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of TRIDIL. If pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension, and the pulmonary capillary wedge pressure is thus a useful guide to safe titration of the drug.

Carcinogenesis, mutagenesis, impairment of fertility

No long-term studies in animals were performed to evaluate carcinogenic potential of TRIDIL.

Pregnancy

Category C. Animal reproduction studies have not been conducted with TRIDIL. It is also not known whether TRIDIL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TRIDIL should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRIDIL is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of TRIDIL in children have not been established.

ADVERSE REACTIONS

The most frequent adverse reaction in patients treated with TRIDIL is headache, which occurs in approximately 2% of patients. Other adverse reactions occurring in less than 1% of patients are the following: tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain.

The following additional adverse reactions have been reported with the oral and/or topical use of nitroglycerin: cutaneous flushing, weakness, and occasionally drug rash or exfoliative dermatitis.

OVERDOSAGE

Accidental overdosage of TRIDIL may result in severe hypotension and reflex tachycardia which can be treated by elevating the legs and decreasing or temporarily terminating the infusion until the patient's condition stabilizes. Since the duration of the hemodynamic effects following TRIDIL administration is quite short, additional corrective measures are usually not required. However, if further therapy is indicated, administration of an intravenous alpha adrenergic agonist (e.g., methoxamine or phenylephrine) should be considered.

DOSAGE AND ADMINISTRATION

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Some patients with normal or low left ventricular filling pressures or pulmonary capillary wedge pressure (e.g., angina patients without other complications) may be hypersensitive to the effects of TRIDIL and may respond fully to doses as small as 5 mcg/min. These patients require especially careful titration and monitoring.

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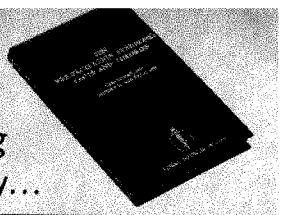

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC

Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC

Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

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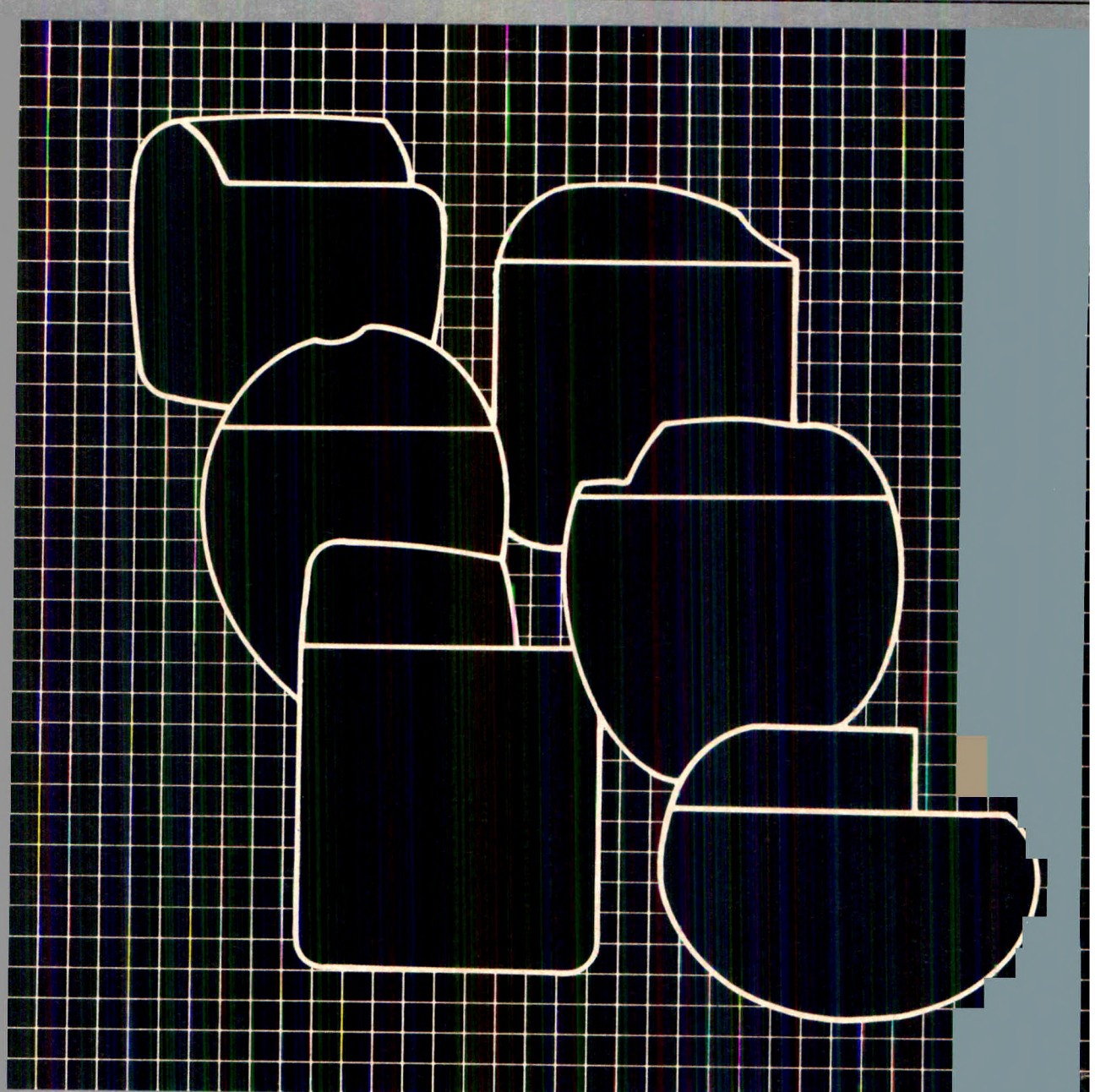

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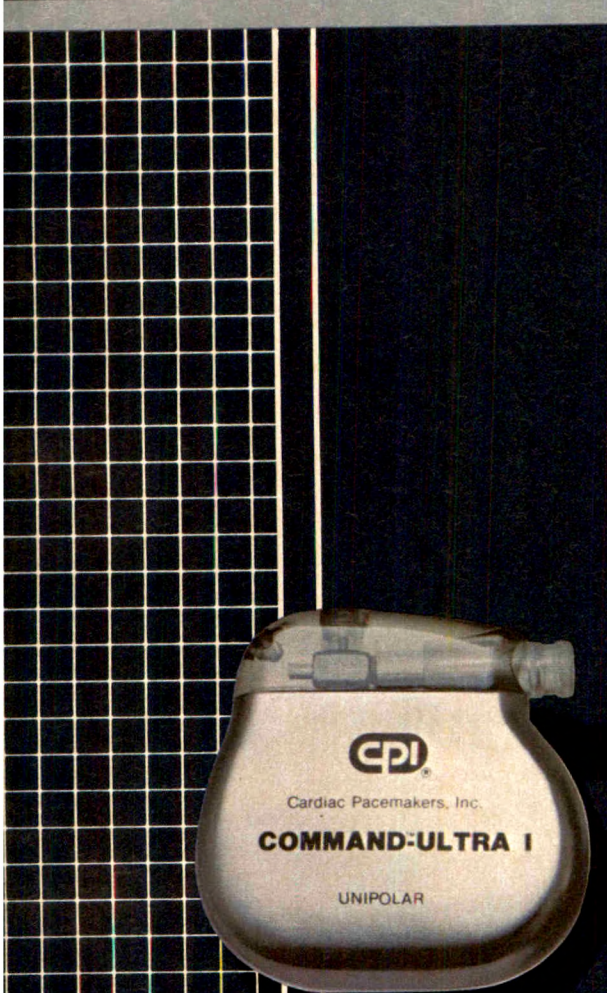

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Ativan®: Agent
(lorazepam)

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it's shorter acting, with brief accumulation

In contrast to long-acting benzodiazepines, Ativan has a short, 12-hour half-life, and no active metabolites. In multiple-dose therapy, Ativan accumulates for only 2 to 3 days before reaching steady state; the long-acting benzodiazepines—diazepam CIV, chlordiazepoxide CIV, clorazepate CIV and prazepam CIV—with their active metabolites accumulate for as long as 20 days before reaching steady state. Cumulative sedative effects are seldom a problem with Ativan.[1]

it doesn't interact with drug metabolized by P450 microsomal enzyme

Most benzodiazepines undergo oxidative metabolis and thus utilize the hepatic microsomal enzyme system. Ativan® (lorazepam), however, is metabolize by glucuronidation and does not compete with other drugs for cytochrome P450. Thus, when Ativa is given with Tagamet® (cimetidine), for example, clearance is not delayed, nor sedation increased*—unlike reported observations with patients on othe benzodiazepines.[2-6]

1. Shader RI, Greenblatt DJ, Ciraulo DA: Psychiatric Annals *11*:16-20, 1981.
2. Klotz U, Reimann I: N Engl J Med *302*:1012-1014, 1980.
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6. Ruffalo RL, Thompson JF, Segal JL: South Med J *74*:1075-1078, 1981.

*All benzodiazepines produce additive effects when given with CNS depressants such as barbiturates or alcohol.

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t gives you greater control of therapy

he short half-life of Ativan® (lorazepam) facilitates nore rapid response to dosage adjustments, llowing you to titrate therapy to patients' changing eeds. Also, once you decide to discontinue Ativan, will be out of your patient's system 4 days after the nal dose—in contrast to long-acting benzodiazepines nd their active metabolites which take as much as weeks to be totally eliminated.

Ativan®
for (lorazepam)℞ Anxiety

Wyeth Laboratories
Philadelphia, PA 19101

See important information on following page.

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan®
for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories
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The Second Issue of the New Annual pr a multidisciplinary approach to the lates important information on the state-of art of cardiovascular medicine and sur

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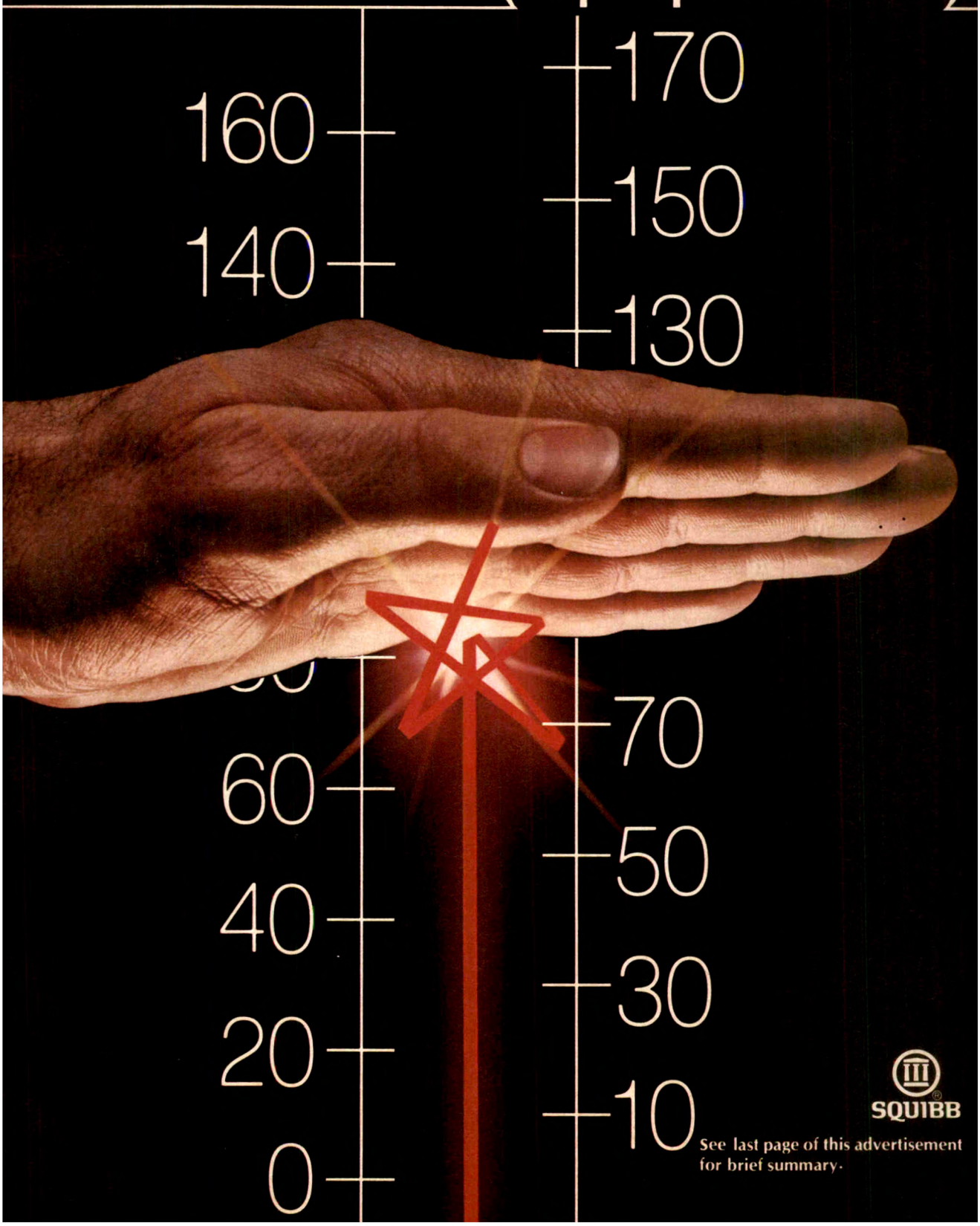
Designed to achieve your therapeutic goals in hypertension

CAPOTEN® (captopril tablets)



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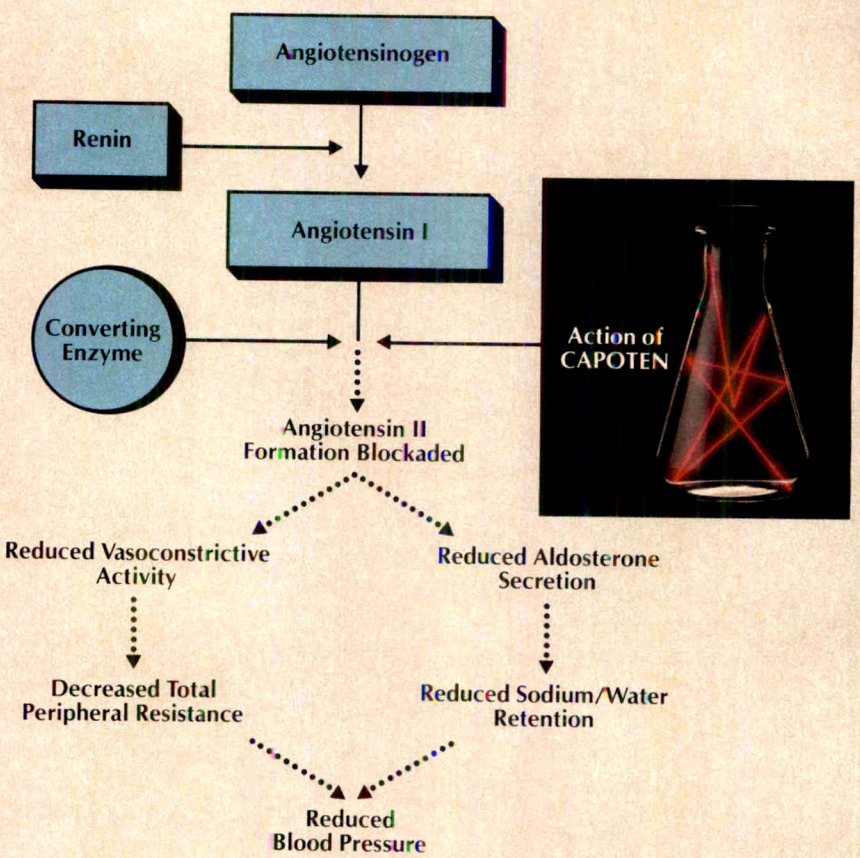
See last page of this advertisement for brief summary.

ACE* INHIBITOR

CAPOTEN® (captopril tablets)

Because of its specific action within the renin-angiotensin-aldosterone (RAA) system, CAPOTEN enables you to reliably control blood pressure in a diverse group of hypertensive patients.



For hypertensive patients:

who experience unacceptable side effects with beta blockers, antiadrenergic agents, or vasodilators

whose blood pressure is uncontrolled by standard multidrug regimens

who have concomitant conditions contraindicating use of other antihypertensive agents

*Angiotensin Converting Enzyme

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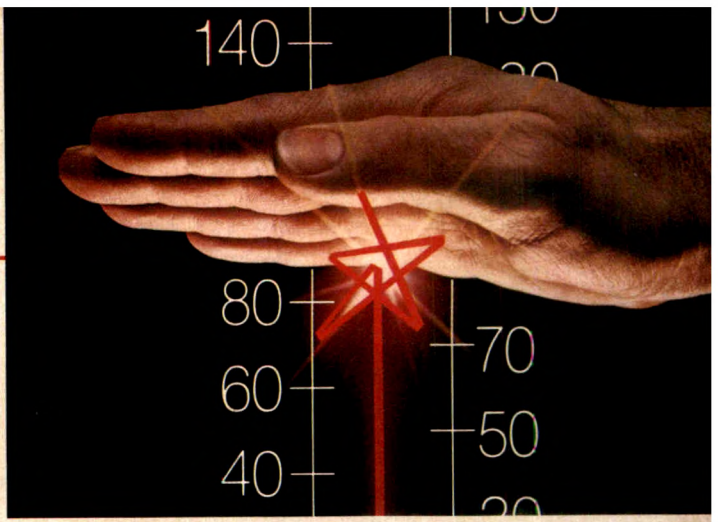

A design that controls blood pressure without the following usual antihypertensive side effects*

- ▶ No cardiac depression
- ▶ No glucose intolerance
- ▶ No bradycardia
- ▶ No mental depression
- ▶ No sleep disturbances
- ▶ No nasal congestion
- ▶ No hypokalemia

- ▶ Rare impotence/loss of libido
- ▶ Rare bronchospasm
- ▶ Rare tachycardia
- ▶ Rare fatigue

ACE INHIBITOR

CAPOTEN®
(captopril tablets)

*Please see brief summary of prescribing information on the last page of this advertisement for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

ACE* INHIBITOR

CAPOTEN® (captopril tablets)

Designed to control blood pressure even when coexisting disorders complicate hypertension management

Unlike some other antihypertensive agents, CAPOTEN is appropriate for use in the presence of a wide range of cardiovascular and metabolic disorders that often coexist with hypertension.

- **Bronchospastic disease**
- **Cardiac arrhythmias**
- **Congestive heart failure**
- **Diabetes mellitus**
- **Hepatic disease**

Designed to control blood pressure when conventional multidrug regimens have proven inadequate

In scores of clinical studies, the effectiveness of CAPOTEN in lowering elevated blood pressure has been proven in many kinds of hypertension—even in those types that are most difficult to treat.

- **Essential hypertension**
- **Hypertension resistant to standard triple therapy (STT)**
- **Hypertension associated with low, normal, and high plasma renin levels**
- **Renovascular hypertension**

*Angiotensin Converting Enzyme

Designed to achieve your therapeutic goals in hypertension

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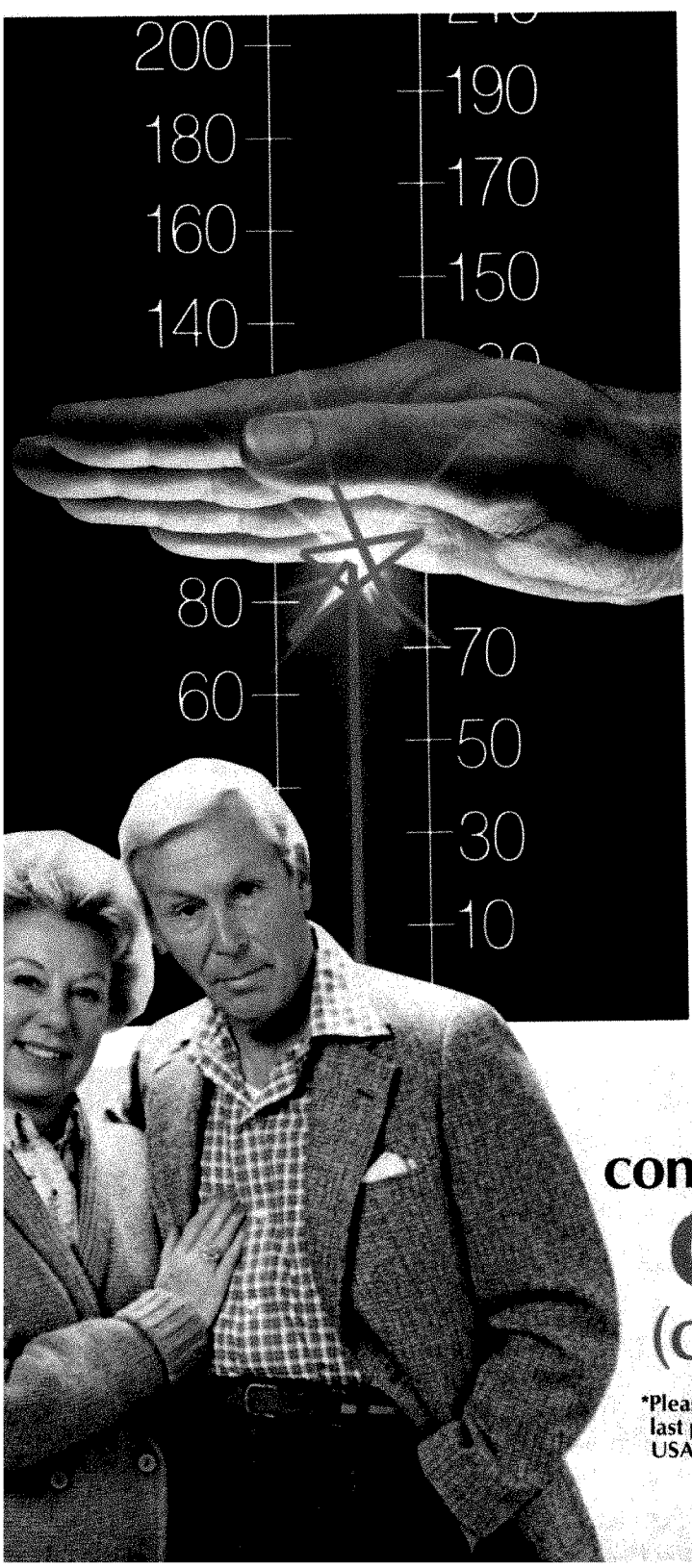

Effective blood pressure control

▶ Routine monitoring procedures are recommended because serious side effects (neutropenia/agranulocytosis, proteinuria) have been associated with CAPOTEN.*

▶ Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.

▶ Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.

▶ Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.

▶ The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

In hypertension... confidence comes with

CAPOTEN®

(captopril tablets)

*Please see brief summary of prescribing information on the last page of this advertisement for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

Captopril Tablets

DESCRIPTION: Capoten (captopril) is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for converting angiotensin I to angiotensin II.

INDICATIONS: Because serious adverse effects have been reported (see WARNINGS), Capoten is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects. Usually, multidrug regimens include combinations of a diuretic, a sympathetic nervous system-active agent (such as a beta-blocker) and a vasodilator.

Capoten (captopril) is effective alone, but in the population described above, it should usually be used in combination with a thiazide-type diuretic. The blood pressure lowering effects of captopril and thiazides appear to be additive.

WARNINGS: Proteinuria—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. Existence of prior renal disease increased the likelihood of development of proteinuria. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued, but some patients had persistent proteinuria. The BUN and creatinine were seldom altered in the proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related; this is uncertain since patients were not biopsied prior to treatment and membranous glomerulopathy may be associated with hypertension in absence of captopril therapy. Since most cases of proteinuria occurred by the 8th month of captopril therapy, patients on captopril should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis—Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller, and it is sufficient in these patients to have white blood cell counts every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in severely salt/volume depleted persons such as those treated vigorously with diuretics, e.g., patients with severe congestive heart failure (see PRECAUTIONS [Drug Interactions]).

PRECAUTIONS: General: *Impaired Renal Function*—Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible (see DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]). *Surgery/Anesthesia*—During major surgery or anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release; if hypotension occurs and is considered due to this mechanism, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy*—A precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretic therapy and those on severe dietary salt restriction or dialysis. The possibility of hypotensive effects can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose. If hypotension occurs, place the patient in a supine position and, if necessary, administer an I.V. infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Since captopril decreases aldosterone production, elevation of serum potassium may occur. Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. If the patient has received spironolactone at any time up to several months prior to captopril therapy, determine the serum potassium frequently since the effect of spironolactone persists.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential.

Animal Toxicology: Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and variation of retinal blood vessels. Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses 50 to 150 times the maximum recommended human dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8 to 30 times MRHD. The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8 to 30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 and 30 times MRHD and thrombocytopenia at 30 times MRHD. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacri-

[illegible] in a moribund condition in the 1 year study. However, in the 47-week study at a 30 times MRHD, bone marrow suppression was found to be reversible upon conti drug administration. Captopril caused hyperplasia of the juxtaglomerular apparatus c kidneys at doses 7 to 200 times the MRHD in rats and mice, at 20 to 60 times M in monkeys, and at 30 times the MRHD in dogs. Gastric erosions/ulcerations wer creased in incidence at 20 and 200 times MRHD in male rats and at 30 and 65 times M in dogs and monkeys, respectively. Rabbits developed gastric and intestinal ulcers given oral doses about 30 times MRHD for only 5 to 7 days. In the two-year rat study, versible and progressive variations in the caliber of retinal vessels (focal saccula and constrictions) occurred at all dose levels (7 to 200 times MRHD) in a dose-re fashion. The effect was first observed in the 88th week of dosing, with a progress increased incidence thereafter, even after cessation of dosing.

Pregnancy: Category C—Captopril was embryocidal in rabbits when given in doses 2 t times (on a mg/kg basis) the maximum recommended human dose. The marked bryocidal effect in rabbits was most probably due to the particularly marked decr in blood pressure caused by the drug in this species. Captopril given to pregnant ra 400 times the recommended human dose continuously during gestation and lacta reduced neonatal survival. No teratogenic effects (malformations) have been seen large doses of captopril in hamsters, rats, and rabbits.

There are no adequate and well-controlled studies in pregnant women. Capt should be used during pregnancy only if the potential benefit justifies the potential to the fetus.

Nursing Mothers: Concentrations of captopril in human milk are about 1% of thos maternal blood. The effect of low levels of captopril on the nursing infant has not b determined. Exercise caution when administering captopril to a nursing woman, an general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established altho there is limited experience with use of captopril in children from 2 months to 15 y of age with secondary hypertension and varying degrees of renal insufficiency. Dos on a weight basis, was comparable to that used in adults. Captopril should be use children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving a 4000 patients.

Renal—One to 2 of 100 patients developed proteinuria (see WARNINGS). Rena sufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 pati but relationship to drug use is uncertain.

Hematologic—Neutropenia/agranulocytosis (probably drug related) occurred in al 0.3% of captopril treated patients (see WARNINGS). Two of these patients develc sepsis and died.

Dermatologic—Rash (usually maculopapular, rarely urticarial), often with pruritus sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 4 weeks of therapy. The rash is usually mild and disappears within a few days of dos reduction, short-term treatment with an antihistaminic agent, and/or discontinuing t apy; remission may occur even if captopril is continued. Pruritus, without rash, in al 2 of 100 patients. Between 7 and 10% of patients with skin rash have shown an eos philia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, photosensitivity have also been reported. Angioedema of the face, mucous membra of the mouth, or of the extremities in about 1 of 100 patients—reversible on discon ance of captopril therapy. One case of laryngeal edema reported. Flushing or pallc 2 to 5 of 1000 patients.

Cardiovascular—Hypotension in about 2 of 100 patients. See PRECAUTIONS (D Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycar chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocar infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1 patients.

Dysgeusia—About 7 of 100 patients developed a diminution or loss of taste per tion; taste impairment is reversible and usually self-limited even with continued drug (2 to 3 months). Weight loss may be associated with the loss of taste. Gastric irritat abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulc peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, paresthesias reported in about 0.5 to 2% of patients but did not appear at increa frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although causal relationship has been established. A single case of hepatocellular injury secondary cholestasis has been reported in association with captopril use. A trans elevation of BUN and serum creatinine may occur, especially in volume-depleted or re vascular hypertensive patients. In instances of rapid reduction of longstanding or seve elevated blood pressure, the glomerular filtration rate may decrease transiently, resulting in transient rises in serum creatinine and BUN. Small increases in serum po sium concentration frequently occur, especially in patients with renal impairment (PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with I.V. infusion of normal saline is the treatment of choice for restoration of blood p sure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour bef meals. Dosage must be individualized.

Give consideration to recent antihypertensive drug therapy, extent of blood press elevation, salt restriction, and other circumstances before initiating therapy. If possi discontinue the patient's previous antihypertensive drug regimen for one week bef starting captopril. Initial dose of CAPOTEN (captopril) is 25 mg t.i.d. If satisfactory bl pressure reduction is not achieved after 1 or 2 weeks, dose may be increased to 50 t.i.d. If the blood pressure has not been satisfactorily controlled after another 1 to 2 wee add a modest dose of a thiazide-type diuretic (e.g., hydrochlorothiazide, 25 mg dai The diuretic dose may be increased at 1- to 2-week intervals until its highest usual a hypertensive dose is reached. If further blood pressure reduction is required, CAPOT (captopril) may be increased to 100 mg t.i.d. and then, if necessary, to 150 mg t. (while continuing the diuretic). The usual dose range is 25 to 150 mg t.i.d. A maxim daily dose of 450 mg CAPOTEN (captopril) should not be exceeded.

For patients with accelerated or malignant hypertension, when temporary discontin tion of current antihypertensive therapy is not practical, or when prompt titration to m normotensive blood pressure levels is indicated, current antihypertensive medication n be stopped and CAPOTEN (captopril) dosage promptly initiated at 25 mg t.i.d., under cl medical supervision. The daily dose of CAPOTEN (captopril) may be increased every hours until a satisfactory blood pressure response is obtained or the maximum capto dose is reached. In this regimen, addition of a more potent diuretic, e.g., furosemi may also be indicated. Beta-blockers may also be used in conjunction with capto therapy (see PRECAUTIONS [Drug Interactions]), but the effects of the 2 drugs are l than additive.

Dosage Adjustment in Renal Impairment—Because CAPOTEN (captopril) is excret primarily by the kidneys, excretion rates are reduced in patients with impaired renal fu tion. These patients will take longer to reach steady-state captopril levels and will rea higher steady-state captopril levels for a given daily dose than patients with normal re function. Therefore, these patients may respond to smaller or less frequent doses. cordingly, for patients with significant renal impairment, initial daily dosage of CAPOT (captopril) should be reduced, and smaller increments utilized for titration, which sho be quite slow (1- to 2-week intervals). After desired therapeutic effect has been achiev dose should be slowly back-titrated to determine minimal effective dose. When c comitant diuretic therapy is required, a loop diuretic (e.g., furosemide), rather thar thiazide diuretic, is preferred in patients with severe renal impairment.

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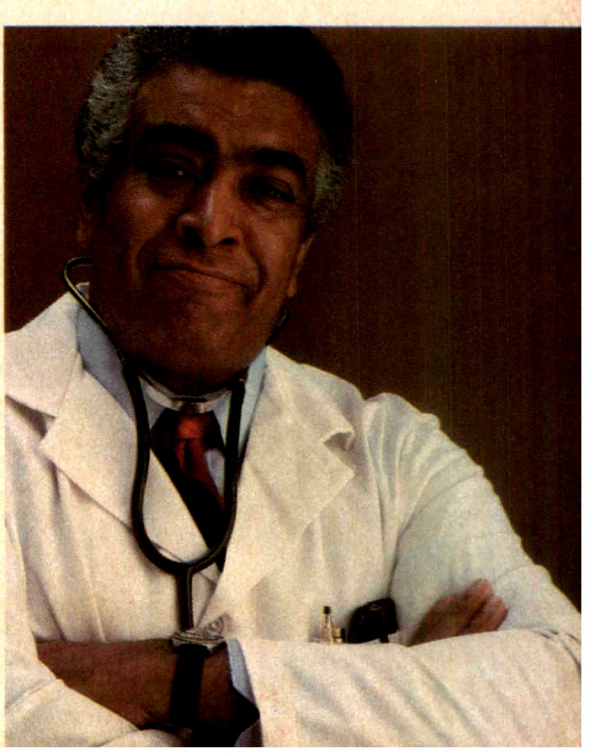

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KLOTRIX®
(POTASSIUM CHLORIDE) SLOW-RELEASE TABLETS, 10 mEq

DESCRIPTION KLOTRIX is a film-coated (not enteric-coated) tablet containing 750 mg potassium chloride (equivalent to 10 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS—BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with potassium-sparing diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. KLOTRIX is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. KLOTRIX should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram and clinical status of patient.

ADVERSE REACTIONS Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose. One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.

Note: KLOTRIX® slow-release tablets must be swallowed whole and never crushed or chewed. Following release of the potassium chloride, the expended wax matrix, which is not absorbed, may be observed in the stool.

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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before Calan is used. Calan may occasionally produce hypotension usually asymptomatic, orthostatic, mild, and controlled by decrease in Calan dose. Occasional elevations of liver enzymes have been reported; patients receiving verapamil should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) may develop a very rapid ventricular response after receiving verapamil (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil. **Precautions:** Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of Calan and beta-blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, verapamil should be used alone if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with verapamil and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic verapamil treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil may have an additive hypotensive effect in patients receiving blood-pressure lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd-degree (0.8%), bradycardia: HR < 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, maculae, and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients. **How Supplied:** Calan (verapamil HCl) is supplied in 80-mg and 120-mg sugar-coated tablets.

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NOSOCOMIAL INFECTIONS

edited by
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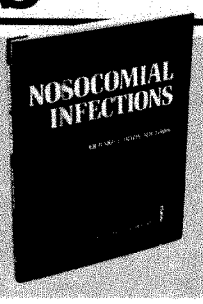

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MILTON PACKER, MD, Guest Editor, and WILLIAM H. FRISHMAN, MD, Guest Co-Editor

Verapamil Therapy for Stable and Unstable Angina Pectoris: Calcium Channel Antagonists in Perspective

MILTON PACKER, MD, and WILLIAM H. FRISHMAN, MD

The papers that comprise this symposium summarize the international experience with verapamil in the management of patients with stable and unstable angina pectoris. These data formed the basis of approval of verapamil for the treatment of angina pectoris by the Cardio-Renal Advisory Committee of the Food and Drug Administration (FDA) in August 1981.

Symposium Perspective

Goal of the symposium: One year ago, we asked each investigator who presented data to the FDA to write a definitive review of a particular aspect of verapamil therapy, in which he would not only present his own data in a detailed and yet concise format, but also summarize the world's literature relevant to that specific topic. It was our impression that, although much had been written about verapamil, there was no central source of information and no consensus as to its role as an antianginal agent. The drug had been in clinical use for nearly 20 years, but most of the well-controlled data establishing its effectiveness had only become available within the last 3 years; clinicians were well aware of the anecdotal reports that dominated the literature 10 years ago, but the more recent well-controlled studies appeared to have received little attention. As a result, when planning this symposium, we asked each investigator to make each manuscript a timely critical review. When discussing pharmacology and drug interactions, we wanted only those data derived from studies using objective methods and controlled study designs. When discussing clinical efficacy, we wanted only conclusions based on randomized double-blind placebo-controlled trials. We asked each author to emphasize not only verapamil's advantages but its disadvantages; to underscore not only those clinical settings when the drug should be used, but also when it should be avoided. Our goal was to create a perspective, solidly based on concrete data and immediately translatable into clinical use.

The result is this symposium. Within its individual manuscripts we have effectively collected the world's experience on the *clinical* use of verapamil in ischemic heart disease into a single central source. Every paper in this symposium contains data obtained from patients enrolled in randomized clinical trials; in 9 papers, nearly all data presented is double-blind and placebo- or propranolol-controlled.

This symposium is divided into three parts; the first two appear in this month's issue and the third will appear in the November issue. The first part deals with the clinical pharmacology of verapamil, the second with its use in patients with angina at rest, and the third with its efficacy in patients with effort-related symptoms. The effectiveness of verapamil in the management of patients with supraventricular arrhythmias and hypertrophic cardiomyopathy is not specifically addressed.

From the Divisions of Cardiology, Departments of Medicine, The Mount Sinai School of Medicine, New York, New York; and the Albert Einstein School of Medicine, Bronx, New York.

Dr. Packer is the recipient of a Young Investigator's Research Award R23-HL-25055-02 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Dr. Frishman is a Teaching Scholar of the American Heart Association, Dallas, Texas.

Address for reprints: Milton Packer, MD, Division of Cardiology, The Mount Sinai Medical Center, 1 Gustave Levy Place, New York, New York 10029.

Verapamil: Pharmacologic and Hemodynamic Actions and Interactions

Historical perspective: First synthesized in 1962,[1] verapamil was the first compound described with the ability to selectively inhibit the transmembrane flux of calcium ions in excitable tissues.[2] Although initially believed to be a beta-adrenergic blocking drug,[3] it was found to exert peripheral and coronary vasodilator effects,[4] and thus underwent early evaluation as an antianginal agent[5]; subsequent studies demonstrated that the drug also had significant antiarrhythmic properties when tested in a variety of experimental preparations.[6] After 20 years, verapamil has emerged in the research laboratory as a valuable agent in the study of the role of the slow channel in the genesis of cardiac arrhythmias and as a chemical probe in studies of excitation-secretion and excitation-contraction coupling. In the clinical sphere, the drug has proved to have beneficial effects in the treatment of angina pectoris and supraventricular tachyarrhythmias.

Mechanism of antianginal effect: The mechanism of verapamil's antianginal actions appears highly complex. As discussed by Singh et al. in the first paper of this symposium, verapamil exerts vasodilator effects on the coronary and peripheral vessels as well as depressant effects on cardiac contractility and conduction; all four actions may be important in mediating the drug's antianginal effects. Verapamil is only a *mild* dilator of epicardial coronary vessels not in spasm, but the drug greatly attenuates sympathetically mediated and ergonovine-induced coronary vasoconstriction; these actions provide a rational basis for the drug's effectiveness in vasospastic ischemic syndromes. In patients with exertional anginal pectoris, verapamil's peripheral vasodilator actions and inhibitory effects on the sinus node serve to attenuate the increases in double product that normally accompany, and serve to limit, exercise. In addition, verapamil appears to exert effects on contractility, on stenosis diameter, and on ventricular compliance that may play important contributory roles in mediating its clinical benefits in ischemic heart disease.

Clinical significance of negative inotropic effects: The importance of verapamil's negative inotropic effects also is addressed by Singh et al. In patients with normal or moderately reduced ventricular function, verapamil's ability to reduce afterload likely counteracts its intrinsic negative inotropic effects, and thus, verapamil therapy is accompanied by little change in cardiac performance. However, in patients with a severely reduced left ventricular ejection fraction (less than 30 to 35%), the drug may produce hemodynamic deterioration.

Do these hemodynamic effects of verapamil differ from those of other calcium antagonists, such as nifedipine? Both drugs exert negative inotropic effects in isolated cardiac preparations,[7–9] but many cardiologists regard nifedipine as being less cardiodepressant, either because it is thought to possess less marked effects on cardiac contractility or because it may exert greater systemic vasodilator actions; the greater such vasodilator effects, the more complete is the neutralization of a drug's negative inotropic actions.[10] Although such beliefs concerning the relative effects of verapamil and nifedipine on cardiac performance may indeed be true, there are few comparative clinical data to support these views.

Much of the impression that verapamil exerts clinically important cardiac depressant effects may be a consequence of historical perspective. Because of its effectiveness in controlling supraventricular tachyarrhythmias, verapamil was commonly used (in the past) in patients with severely depressed ventricular function, who were particularly prone to experience such arrhythmias; although we now know that such use is inappropriate, the administration of verapamil to these patients occasionally produced severe exacerbations of heart failure.[11–14] Nifedipine, which has no antiarrhythmic actions, was not used in these clinical settings, and hence, little experience was gained with the use of this drug in patients with very poor cardiac function. Although nifedipine has been used as a vasodilator agent to improve cardiac performance in patients with symptoms of heart failure,[15,16] most of the patients treated in these studies had a left ventricular ejection fraction *greater* than 30% or a normal cardiac output and left ventricular filling pressure at rest; in such patients, neither verapamil nor nifedipine produces a decline in cardiac performance, and both drugs are usually well-tolerated. At Mount Sinai Hospital, using invasive monitoring techniques, both verapamil and nifedipine have been evaluated in patients with severe angina pectoris and an ejection fraction *less* than 30%. Although both drugs were well tolerated in most of these patients, worsening of ventricular performance was occasionally noted with both verapamil and nifedipine. Clearly, more work needs to be done to elucidate the safety and effectiveness of calcium antagonists in general in patients with severe left ventricular failure; until such data are available, we would advise caution with the use of all calcium channel blocking agents in such individuals.

Verapamil drug interactions: The next two papers in this issue review important interactions between verapamil and other cardiovascular agents. In the only report in this symposium which discusses the use of verapamil in the management of tachyarrhythmias, Klein and Kaplinsky review the interaction between verapamil and digitalis. Although digitalis has long been the principal drug used in patients with atrial fibrillation, the drug does not block the excessive ventricular rates that are seen in such patients during exercise. In contrast, verapamil effectively attenuates this excessive ventricular response and improves exercise capacity in such patients; when combined, the effects of verapamil and digoxin appear to be additive.

Verapamil increases serum digoxin levels in patients with atrial fibrillation. The mechanisms underlying this effect are similar to those proposed to explain the similar increase that accompanies the institution of quinidine therapy: a reduction in renal tubular secretion, in

metabolic clearance, and in the volume of distribution of digoxin.[17–19] However, the benefits of combined digoxin-verapamil therapy in patients with atrial fibrillation (previously outlined) are not a consequence of an increase in serum digoxin levels, because they are not reproduced by doubling the dose of digoxin in the absence of verapamil therapy. Recent evidence that nifedipine also increases serum digoxin levels[20] suggests that the renal or nonrenal clearance, or both, of digoxin may be mediated by calcium-dependent mechanisms. Hence, careful reassessment of digitalis therapy is needed whenever combined use of digitalis and calcium antagonists is contemplated.

Because both drugs possess negative chronotropic and inotropic effects, combined therapy of beta-adrenergic blocking drugs and verapamil has long been avoided. Packer et al. review the results of five hemodynamic and clinical studies concerning this interaction. The available evidence suggests that few cardiodepressant effects are seen when combined therapy of verapamil and low or moderate doses of propranolol are used; however, additive negative inotropic and chronotropic effects *are* observed when verapamil is administered to patients receiving large doses of propranolol. This appears to be particularly significant in patients with compromised left ventricular function (ejection fraction less than 30%) or in those taking drugs that attenuate alpha-adrenergic responses (for example, methyldopa). In patients who tolerate combined therapy, the benefits of such treatment are greater than those observed with the administration of either agent used alone. Although some have feared that verapamil would produce additive or synergistic effects on atrioventricular conduction, this has rarely been observed; adverse reactions appear largely hemodynamic rather than electrophysiologic. Because combined therapy of nifedipine and beta-blocking agents has also been reported to exacerbate clinical heart failure,[21,22] it appears prudent to exercise caution whenever combined calcium channel and beta-adrenergic blockade is used in the treatment of ischemic heart disease. Further large-scale studies are needed to determine the safety and efficacy of this therapeutic approach.

Verapamil: Studies in Angina at Rest

Verapamil versus placebo: Patients with angina at rest may have a wide spectrum of disorders, ranging from variant angina (S-T elevation) associated with angiographically normal coronary arteries to unstable angina with S-T depression or elevation associated with multivessel coronary artery disease. The elegant studies of Maseri et al.[23] suggest that coronary vasospasm plays a major role in the pathogenesis of ischemia in most patients with angina at rest, regardless of the coronary anatomy. Verapamil might therefore be expected to be effective in this syndrome because of its ability to block spontaneous and drug-induced spasm.[24] Such expectations are borne out by the double-blind placebo-controlled randomized trials reviewed by the three papers that comprise Part II. In a 9 month double-blind crossover trial, Winniford and co-workers demonstrate the effectiveness of verapamil in patients with variant angina, most of whom had normal coronary arteries. In two shorter but carefully controlled blinded trials, Mehta et al. and Parodi et al. establish verapamil's effectiveness in patients with unstable angina associated with severe obstructive coronary artery disease. In all three studies, verapamil not only greatly reduced the frequency of anginal attacks and the consumption of nitroglycerin but also decreased the total number of ischemic episodes as assessed by continuous Holter monitoring.

Verapamil versus propranolol and nifedipine: How does verapamil compare with other drugs advocated for the management of patients with angina at rest, such as propranolol and nifedipine? Parodi et al. address the comparative efficacy of verapamil and propranolol in their randomized blinded crossover trial. Only verapamil reduced symptomatic and asymptomatic episodes of ischemia; the effectiveness of propranolol was comparable with that of placebo. These findings are consistent with the concept that coronary vasospasm plays a crucial role in patients with angina at rest; in contrast, rather than provide any benefit, propranolol may exacerbate vasospastic phenomena.[25]

Winniford et al. directly address the comparative efficacy of verapamil and nifedipine in their report; a subset of their patients with variant angina received open-label nifedipine after completion of the placebo-controlled trial with verapamil. Both verapamil and nifedipine proved equally effective, and neither drug depressed ventricular function, either at rest or during exercise. However, adverse effects (headache, hypotension, and dizziness) occurred more frequently with nifedipine than with verapamil, and these reactions limited the dose of nifedipine that could be administered. These data indicate that in the management of patients with variant angina, the choice of a calcium antagonist is likely to be determined not so much by which drug is more effective, but by which agent is better tolerated by an individual patient.

Verapamil: Studies in Effort-Related Angina

Verapamil versus placebo: In Part III of this Symposium (to appear in the November issue) Weiner and Klein review the evidence derived from 6 independent double-blind placebo-controlled trials involving 193 patients and conclude that verapamil is a highly effective and safe drug for the treatment of exertional anginal discomfort.

Verapamil versus beta-blocking drugs: How does verapamil compare with other therapies advocated for the treatment of effort-related anginal symptoms? In their review of 9 double-blind randomized crossover trials, which compared verapamil therapy to treatment with beta-blocking drugs in 174 patients, Bala Subramanian et al. conclude that verapamil is as safe and effective as beta-blocking drugs in the treatment of patients with stable angina pectoris. In many studies cited, particularly those performed within the last 3 years, verapamil was superior to propranolol in prolonging the

duration of exercise. However, one must consider the possibility that patients entered into such recent studies were those who agreed to be subjects because they remained symptomatic despite previous therapy, which likely included a beta-blocking drug; this may have biased these trials toward finding a more favorable effect of verapamil.

In attempting to choose between verapamil and propranolol in the management of patients with effort-related symptoms, clinicians should keep in mind that some patients with angina do better with one drug than with the other. Unfortunately, we know little about how to predict with confidence the superior agent in a specific patient short of a therapeutic trial. In general however, verapamil can be used as an effective alternative in patients who remain symptomatic despite therapy with propranolol and as a first-line antianginal drug in patients with contraindications to beta-blockade.

As Frishman et al. point out, both verapamil and propranolol may be useful in the treatment of patients with both systemic hypertension and angina pectoris. Indeed, because of its peripheral vasodilator properties, verapamil may prove to be the superior antihypertensive agent. Because its long-term administration is well tolerated, verapamil merits further study in the management of patients with hypertension with and without coronary artery disease.

Verapamil versus nifedipine: Bala Subramanian et al. directly address the comparative effectiveness of verapamil and nifedipine in effort-related angina. In a double-blind randomized crossover trial involving 32 patients with stable anginal symptoms, verapamil was superior to nifedipine in prolonging exercise duration when either agent was used alone. Furthermore, verapamil was better tolerated than was nifedipine; 7 patients had increasing angina while taking nifedipine, whereas none did so while taking verapamil. A potential limitation of this study is that it used fixed doses of both drugs; however, the dose of nifedipine used (60 mg daily) was identical to that employed in the multicenter placebo-controlled trials of nifedipine recently conducted in the USA,[26] and the dose of verapamil used (360 mg daily) was similar to that administered in previous placebo-controlled evaluations. Larger doses of nifedipine might have produced greater effects, but such doses may have produced even more frequent adverse reactions. The authors conclude that verapamil is superior to and safer than nifedipine, when either drug is used alone in the treatment of exertional angina.

The finding that verapamil produces fewer adverse reactions than nifedipine is similar to the results of Winniford et al. reported earlier in this symposium. The two groups differ, however, in the types of side effects noted. Whereas the reactions noted by Winniford et al. (headache, hypotension, palpitations, peripheral edema) frequently required discontinuation of the drug or a reduction in dose, they were not life-threatening. Bala Subramanian et al., on the other hand, observed patients in whom therapy with nifedipine provoked episodes of ischemia. These differences may be attributable to differences in the patient populations evaluated; whereas most of the patients of Winniford et al. had normal coronary arteries, most of the patients of Bala Subramanian et al. probably had multivessel coronary artery disease. The greater frequency of adverse effects with nifedipine was recently confirmed by Dawson et al.[27] in a double-blind comparison of verapamil and nifedipine in patients with chronic stable angina; however, the types of adverse effects noted by these investigators were similar to those noted by Winniford et al.

The differences between nifedipine and verapamil noted by Bala Subramanian et al. may be the consequence of differences in their pharmacologic actions. Whereas both drugs exert antianginal effects by virtue of their peripheral vasodilator actions, such systemic vasodilation provokes sympathetically mediated reflex tachycardia, which (if left unopposed) might detract from a drug's antianginal effects and provoke adverse reactions (palpitations, headaches, and angina). This reflex sympathetic activation is not altered by nifedipine but is attenuated by verapamil, both directly by its inhibitory action on the sino-atrial node[28] and indirectly by a nonspecific antagonist effect on the sympathetic nervous system.[10] Although some view verapamil's effects on the cardiac conduction system as disadvantageous, such effects may contribute to the antianginal efficacy of the drug. On the other hand, optimal therapy with nifedipine in patients with effort-related angina appears to require combined treatment with a beta-blocking agent.

The relative effectiveness of verapamil and nifedipine in the treatment of patients with effort-related angina is likely to remain controversial. Whereas Bala Subramanian et al. found verapamil superior to nifedipine, Dawson et al.[27] found the two drugs equally effective in reducing the frequency of anginal attacks and in prolonging the duration of exercise. Both trials were double-blind and administered similar doses of both agents. The major limitation of both studies, however, is that the investigators compared the effectiveness of verapamil and nifedipine when either agent was used alone. In view of the widespread use of beta-blocking drugs, both in the management of anginal symptoms and in the prevention of future ischemic events in patients recovering from a myocardial infarction,[29] an important question remains regarding the relative efficacy and safety of verapamil and nifedipine when administered to patients receiving beta-adrenergic blocking agents. The choice of a first-line calcium antagonist in the management of patients with effort-related angina awaits the completion of such randomized comparative trials.

Clinical application of verapamil: The last three reports in this symposium review special topics of importance in the clinical use of verapamil in the individual patient with angina pectoris.

In examining the relationship between its antianginal effect and plasma levels of verapamil, Frishman et al. suggest that the optimal dose of verapamil in the management of patients with stable angina pectoris may be

either 320 mg daily (80 mg four times daily) or 360 mg daily (120 mg three times daily). As Pine et al.[30] have demonstrated, increments in the dose of verapamil beyond 360 mg daily is accompanied by only minor further improvements in exercise tolerance and are not infrequently accompanied by a significant increase in adverse reactions. Our own preference is to begin verapamil therapy with a dose of 80 mg four times daily and, if this proves effective, to alter the regimen to 120 mg three times daily in an effort to enhance patient compliance. Whether such observations and conclusions are applicable to the patient with angina at rest is unknown.

Scheidt et al. address the question of verapamil's long-term antianginal effectiveness. Long-term studies, by their very nature, are usually anecdotal because it is difficult to maintain placebo controls for long periods once a therapeutic intervention has been shown effective in an individual patient. This study attempts to improve on the usual anecdotal format by following up 66 patients, in whom the effectiveness of verapamil had been established in randomized double-blind crossover trials and who were then treated for 1 year. The beneficial effects of verapamil in most patients with stable angina pectoris in this study were maintained throughout the period of follow-up. In 21 patients these sustained effects were demonstrated by objective tests of exercise tolerance over the entire 12 months, and exercise tolerance deteriorated when verapamil therapy was discontinued.

The comparative effects of abrupt withdrawal of verapamil and propranolol are compared by Frishman et al. in the final report in the symposium. Of their patients with stable effort-related symptoms, 10% had a severe clinical exacerbation of the anginal syndrome on withdrawal of propranolol; no patient had rebound symptoms when verapamil was abruptly discontinued.

Acknowledgment

We would like to express our great appreciation to the Knoll Pharmaceutical Company, who not only sponsored the publication of this symposium, but more importantly, supported the clinical investigations and trials that constitute the content of these reports. We are also greatly indebted to Dr. Simon Dack, who advised, inspired, and supported us through the difficult task of compiling and editing this work.

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Pharmacologic and Hemodynamic Mechanisms Underlying The Antianginal Actions of Verapamil

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The pharmacologic and hemodynamic effects of verapamil are the result of its selective inhibitory action on the slow channel in cardiac muscle and its propensity to block transmembrane calcium influx in vascular smooth muscle and to nonspecifically antagonize sympathetic excitation. In patients with normal or moderately reduced ventricular function, verapamil's ability to reduce afterload counteracts its intrinsic negative inotropic effects and therefore a reduction in ventricular performance is not seen. In patients with a severely reduced ventricular ejection fraction and high ventricular filling pressures, however, the drug may produce clinical and hemodynamic deterioration. Computer-assisted angiographic analysis shows that verapamil dilates normal as well as narrowed epicardial coronary vessels and reverses ergonovine- and sympathetically provoked coronary vasoconstriction. Intravenous administration of verapamil reduces coronary arterial resistance and enhances coronary sinus flow with variable effects on myocardial oxygen consumption. The drug prevents the ischemic consequences of angina produced by atrial pacing; after verapamil administration, pacing-induced lactate production is lessened, and ischemia-related declines in left ventricular ejection fraction are prevented. During chronic therapy the effects of verapamil on regional and global ventricular function are similar to those of propranolol during supine bicycle exercise. However, verapamil has significantly less effect on rate-pressure product at rest and during exercise, which suggests that its antianginal mechanism of action, unlike that of beta-blocking agents, may not be related solely to a reduction in oxygen demand. These data indicate that the mechanisms underlying the antianginal effects of verapamil are complex and are likely to be multifactorial.

Although verapamil hydrochloride was introduced as a coronary vasodilator and antianginal agent over 20 years ago,[1] only recently has detailed knowledge of its pharmacologic properties become available.[2–4] Verapamil is the prototype of a group of drugs designated as *calcium antagonists* or *slow channel inhibitors*.[2] The delineation of this class of drugs closely followed the demonstration in cardiac muscle that depolarization during the passage of an electrical impulse is mediated by two discrete current systems. The first is a fast sodium current (fast response) which is selectively inhibited by tetrodotoxin and local anesthetics. The second is a slow current system (slow response) which is carried primarily by calcium and is responsible for excitation-contraction coupling in cardiac muscle. It is the selective inhibition of the slow calcium current that characterizes the fundamental property of the calcium antagonists.[2,5] In the heart, the sinoatrial and atrioventricular nodes are slow channel dependent and are the main loci of action of the slow channel inhibitors. In addition, these agents block the transmembrane flux of calcium in cardiac muscle and vascular smooth muscle, especially in the coronary and peripheral arteries;[6] the precise mechanisms involved in these latter effects are unclear because a slow channel has not been identified in smooth muscle tissues.

In this report the pharmacologic and hemodynamic responses to verapamil are discussed with particular

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TABLE I Hemodynamic Effects of Intravenous Verapamil in Patients With Heart Disease: Comparison of Results From 2 Centers

	Singh and Roche[13] (n = 20)			Ferlinz et al.[16] (n = 20)		
	C	V	p	C	V	p
Heart rate (beats/min)	76 ± 13	80 ± 13	NS	74 ± 12	75 ± 12	NS
Mean arterial pressure (mm Hg)	98 ± 15	86 ± 12	p <0.01	94 ± 17	82 ± 12	<0.001
Right ventricular end-diastolic pressure (mm Hg)	...	...	...	4 ± 2	7 ± 2	<0.001
Left ventricular end-diastolic pressure (mm Hg)	11 ± 4	15 ± 4	p <0.01	12 ± 4	14 ± 4	<0.001
Cardiac index (liters/min/m^2)	3.2 ± 0.7	3.6 ± 0.8	NS	2.8 ± 0.6	3.1 ± 0.7	<0.01
Stroke volume index (ml/beat/m^2)	43 ± 11	43 ± 11	NS	57 ± 12	63 ± 13	<0.025
Systemic vascular resistance (dynes-s-cm^{-5})	1,435 ± 356	1,131 ± 367	p <0.001	1,143 ± 429	1,069 ± 235	NS
Left ventricular dP/dt max (mm Hg/s)	1,343 ± 679	1,007 ± 456	p <0.05	...	...	...
Left ventricular ejection fraction (%)	60 ± 11	...	...	55 ± 16	61 ± 18	<0.01

C = control; V = verapamil.

reference to those features of drug action that provide a framework for understanding the potential mechanisms that underlie its antianginal effects.

Hemodynamic Effects of Verapamil

Pharmacologic considerations: The effects of verapamil in the intact circulation are the result of a complex interplay of the direct effects of the drug on the myocardium and the reflex responses provoked by the action of the drug on peripheral vessels; hence, verapamil's effects in animals and in man are not comparable to those seen in isolated muscle preparations.[2,4,7] In isolated cardiac muscle, verapamil exerts a profound negative inotropic effect and a marked depressant effect on impulse formation and conduction in the sinoatrial and atrioventricular nodes; these in vitro depressant effects can be competitively antagonized by calcium and by catecholamines.[7] Verapamil also exerts systemic and coronary vasodilator effects because of its direct action on potential-dependent and receptor-dependent calcium channels in peripheral vessels.[8] These systemic vasodilator actions elicit activation of reflex sympathetic forces, which serve to offset the direct negative effects of the drug on cardiac contractility and conduction. The structures most likely to exhibit verapamil's direct depressant effects are those with intrinsic disorders of contractility or conduction or those in whom sympathetic influences have been pharmacologically attenuated.[9]

Hemodynamic studies in dogs: In open chest anesthetized dogs, Ross and Jorgensen[10] observed that verapamil exerted notable depressant effects on cardiac performance; however, the hypotensive effects of the drug were related to a concomitant reduction in systemic vascular resistance if the dose of verapamil did not exceed 0.25 mg/kg intravenously. In unanesthetized closed chest dogs, the direct cardiodepressant effects of the drug were less pronounced; verapamil produced dose-dependent peripheral vasodilation with reflex *increases* in myocardial contractility and heart rate.[11] Pretreatment with propranolol attenuated reflex cardiac stimulation but did not alter the peripheral vasodilator responses, indicating that the vascular effects of the drug were mediated through mechanisms independent of peripheral beta-adrenoreceptor stimulation.[12] A direct myocardial depressive action became apparent only when a dose of verapamil greater than 0.3 mg/kg was used.

Hemodynamic studies in stable coronary artery disease: Although a number of hemodynamic studies have evaluated the hemodynamic effects of intravenous verapamil in man,[13–20] detailed hemodynamic studies in patients with cardiac disease only recently have been reported[13,16] (Table I).

Singh and Roche[13] assessed the effects of 10 mg of intravenous verapamil in 20 patients with coronary or rheumatic heart disease. Verapamil produced a moderate decrease in mean arterial pressure consequent to a decline in systemic vascular resistance without a change in cardiac and stroke volume indexes. Cardiac output would normally be expected to increase after any drug-induced decrease in peripheral resistance; failure to observe such an increase after verapamil was likely the result of a moderate direct depressant effect of the drug on myocardial contractility. This effect was evidenced by a drug-induced decrease in left ventricular dP/dt max and an increase in left ventricular end-diastolic pressure (Fig. 1). In a separate study of 20 patients with coronary artery disease, Ferlinz et al.[16] administered verapamil as an 0.1 mg/kg bolus followed by an 0.005 mg/kg/min infusion, and observed systemic hemodynamic changes comparable to those seen by Singh and Roche;[13] however, Ferlinz et al.[16] observed significant increases in cardiac output and left ventricular ejection fraction after verapamil (Table I). Most hemodynamic and ventriculographic studies have not demonstrated an increase in cardiac output and ejection fraction after verapamil administration[14,19,20] and therefore are in agreement with the findings of Singh and Roche.[13]

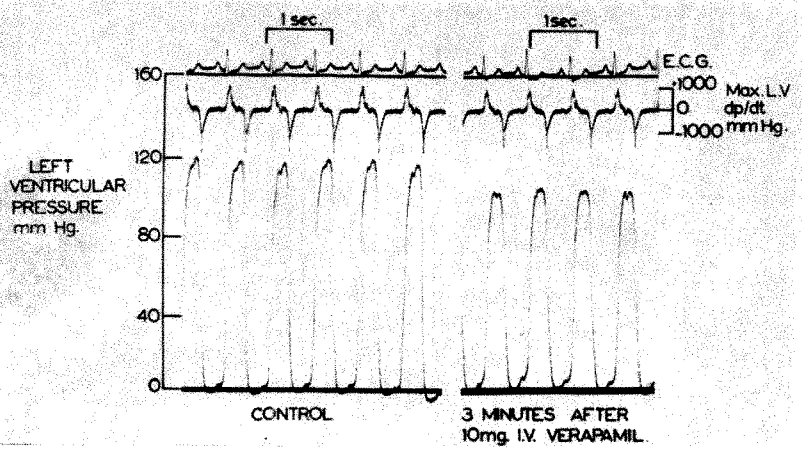

FIGURE 1. Effects of verapamil on left ventricular contractility in a patient with coronary artery disease. The left ventricular pressure and the first derivative of the pressure (LV dP/dt max) were obtained by high fidelity catheter tip manometry and electronic differentiation, respectively. Verapamil diminished peak systolic left ventricular pressure and increased left ventricular end-diastolic pressure, but produced only a small decrease in LV dP/dt max. There was no change in heart rate. (Reproduced, with permission, from Singh and Roche.[13])

It should be emphasized that the two studies just cited were performed in patients with preserved left ventricular function. The left ventricular ejection fractions before verapamil in all of the patients evaluated exceeded 35% and averaged 55 to 60%, and the left ventricular end-diastolic pressures averaged 11 to 12 mm Hg.[13,16] Therefore, in patients without heart failure, the expected myocardial depressant effect of verapamil is largely offset by its vasodilator actions on the peripheral circulation. Although ventricular filling pressures increase modestly after drug administration, cardiac and stroke volume indexes remain unchanged in patients with preserved left ventricular function. These data are consistent with clinical experience that verapamil produces little deleterious hemodynamic effects in patients without cardiac failure.

Verapamil in acute myocardial infarction: Although verapamil has been used to treat supraventricular tachycardia in patients with acute myocardial infarction,[2,4] few detailed hemodynamic studies have been reported in this clinical setting. Chew et al.[14] measured changes in systemic hemodynamics and radionuclide-determined left ventricular ejection fraction after intravenous verapamil (0.145 mg/kg bolus followed by 0.005 mg/kg/min infusion) in 7 patients with acute uncomplicated myocardial infarction (mean pulmonary capillary wedge pressure below 18 mm Hg) and in 15 patients with chronic stable angina without infarction (Table II). The hemodynamic effects of verapamil in the two groups of patients were similar and were comparable to the hemodynamic responses in other studies that evaluated patients with stable coronary artery disease with preserved left ventricular function.[15,16] Therefore, verapamil does not exert a significant cardiac depressant effect in patients with uncomplicated recent myocardial infarction.

The administration of verapamil orally also produces few cardiodepressant effects in patients with acute

TABLE II Hemodynamic Effects of Intravenous Verapamil in Patients With Cardiac Disease (Mean Values ± Standard Deviation)

	Patients With Chronic Angina (n = 15)			Patients With Uncomplicated Acute Myocardial Infarction (n = 7)		
	Pre	Post	p Value	Pre	Post	p Value
Heart rate (beats/min)	74 ± 10	77 ± 11	NS	73 ± 12	78 ± 14	NS
Systolic arterial pressure (mm Hg)	141 ± 15	121 ± 13	<0.001 (−14%)	148 ± 24	121 ± 19	<0.01 (−18%)
Diastolic arterial pressure (mm Hg)	72 ± 20	66 ± 8	<0.001 (−8%)	64 ± 10	58 ± 12	<0.05 (−9%)
Mean arterial pressure (mm Hg)	102 ± 10	86 ± 12	<0.001 (−16%)	90 ± 12	76 ± 15	<0.01 (−16%)
Mean pulmonary arterial pressure (mm Hg)	17 ± 3	18 ± 3	NS	19 ± 4	21 ± 5	NS
Mean pulmonary capillary wedge pressure (mm Hg)	10 ± 2	11 ± 2	<0.01 (+10%)	12 ± 3	14 ± 4	<0.02 (+17%)
Systemic vascular resistance (dynes-s-cm^{-5})	1,424 ± 320	1,100 ± 300	<0.001 (−23%)	1,152 ± 288	896 ± 232	<0.01 (−22%)
Pulmonary vascular resistance (dynes-s-cm^{-5})	240 ± 54	240 ± 50	NS	268 ± 117	256 ± 92	NS
Stroke work index (g-m/m^2)	47 ± 7	41 ± 6	<0.02 (−13%)	42 ± 22	39 ± 11	<0.01 (−7%)
Cardiac index (liters/min/m^2)	2.8 ± 0.4	3.1 ± 0.6	<0.01 (+11%)	2.8 ± 1.3	3.6 ± 0.7	<0.05 (+27%)
Stroke volume index (ml/m^2)	41 ± 10	44 ± 10	<0.01 (+7%)	46 ± 14	48 ± 14	<0.05 (+4%)
Ejection fraction (%)	56 ± 10	56 ± 9	NS	49 ± 16	50 ± 15	NS

NS = not significant; p = probability (significance of difference); post = after verapamil; pre = before verapamil.
Reproduced, with permission, from Chew et al.[14]

myocardial infarction. Theroux et al.[12] evaluated the hemodynamic responses to a single *oral* dose of 160 mg of verapamil in 10 such patients (Fig. 2). Mean arterial pressure decreased moderately without significant effects on heart rate or cardiac index. The data demonstrate that verapamil can safely be administered intravenously or orally in patients with acute myocardial infarction without clinical evidence of cardiac failure.

Verapamil in left ventricular dysfunction: In contrast to the experience just outlined in patients with preserved left ventricular function, Chew et al.[14] showed that verapamil may exert significant cardiodepressant effects in patients with severely impaired left ventricular performance before therapy. In 3 patients with a severely reduced left ventricular ejection fraction (less than 35%) and markedly elevated left ventricular filling pressures (greater than 20 mm Hg), hemodynamic and clinical deterioration occurred after intravenous verapamil administration; mean arterial pressure and cardiac index decreased in association with an abrupt increase in pulmonary capillary wedge pressure (25.7 to 33.3 mm Hg). In contrast, in patients with pulmonary capillary wedge pressures less than 20 mm Hg or a left ventricular ejection fraction greater than 30%, the same doses of intravenous verapamil produced only modest increases in left ventricular filling pressures, no change in left ventricular ejection fraction, and no clinical deterioration. These data indicate that patients with impaired ventricular function are particularly susceptible to verapamil's negative inotropic effects; the reduction in ventricular afterload resulting from the drug's action on peripheral vessels is insufficient to offset the depressant effects of the drug on the myocardium. Verapamil can exacerbate clinical evidence of congestive heart failure and should be used cautiously in patients with a markedly decreased left ventricular ejection fraction (less than 30 to 35%).

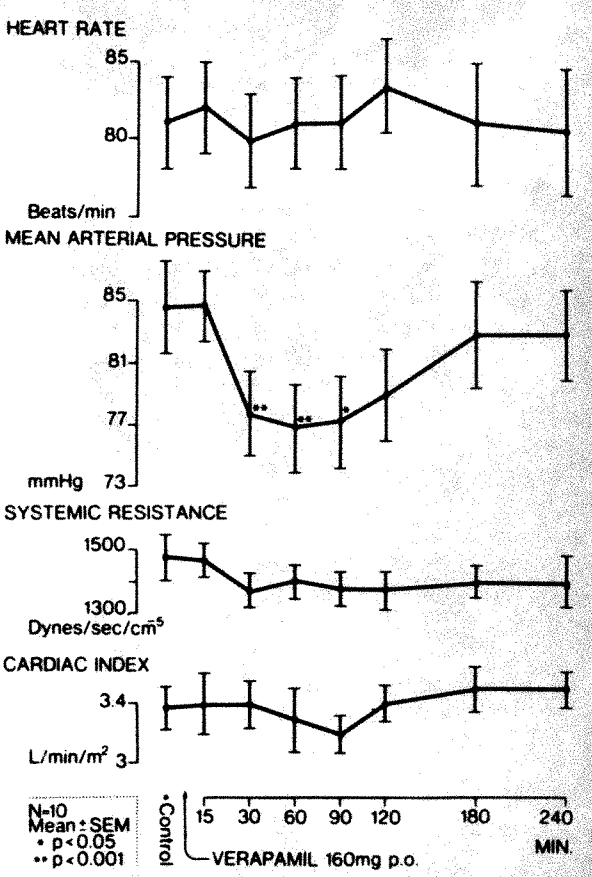

FIGURE 2. Hemodynamic effects of orally administered verapamil (160 mg) in patients with acute myocardial infarction. (Reproduced, with permission, from Theroux et al.[21])

Potential Mechanisms of Antianginal Actions of Verapamil

Primary and secondary angina: Myocardial ischemia occurs when a significant imbalance is created between myocardial oxygen demand and oxygen delivery to the heart. In obstructive coronary artery disease, angina may occur when myocardial oxygen requirements increase secondary to increases in heart rate, blood pressure, ventricular wall tension, or contractility. Because a reduction in coronary blood flow is not the initiating event in such a situation, angina occurring under such conditions has been termed "secondary." Alternatively, angina may result from a "primary" reduction in coronary flow (due to coronary vasospasm) without a change in myocardial oxygen demands and may occur in patients with either normal coronary arteries or those with varying degrees of arteriosclerotic obstruction.[22,23] Most often, primary and secondary angina do not exist as discrete entities; the relationship of the clinical spectrum of myocardial ischemic syndromes and the dynamic pathology of coronary arteriosclerosis was recently emphasized by the quantitative studies of Brown et al.[23,24] To elucidate potential mechanisms of action of antianginal agents, attention must be focused on both drug-induced changes in myocardial oxygen consumption and coronary vasomobility.[25,26]

To obtain insight into the nature of its beneficial actions, three separate studies were performed to examine the effects of verapamil on (1) coronary hemodynamics and vasomobility, (2) pacing-induced myocardial ischemia, and (3) exercise-induced ischemic ventricular dysfunction.

Effects of verapamil on coronary hemodynamics and vasomobility: Verapamil exerts direct vasodilator actions on coronary and systemic vessels in a variety of experimental preparations.[1,27,28] Nayler et al.[12] demonstrated in dogs that verapamil, like propranolol, decreased myocardial oxygen demands; however, whereas propranolol consistently increased coronary vascular resistance, verapamil *decreased* coronary resistance, even during the hypotensive phase of the drug's action.

The effects of verapamil on coronary hemodynamics and vasomobility have been examined in a number of studies in man. Using myocardial clearance of radioactive rubidium as an index of coronary blood flow, Luebs et al.[29] noted a marked increase in coronary blood flow after intravenous verapamil in patients without coronary disease but not in patients with diseased ves-

sels. Simonsen[30] noted that both verapamil and nifedipine reduced coronary arteriolar resistance in patients with coronary artery disease with little or no change in coronary sinus blood flow or myocardial oxygen consumption. In contrast, Ferlinz and Turbow[31] found that in patients with coronary artery disease, intravenous verapamil *decreased* coronary sinus blood flow without significant changes in coronary vascular resistance. They postulated that verapamil exerted its most important effects by reducing systemic vascular resistance and thereby reducing myocardial oxygen consumption; the changes in coronary artery blood flow after verapamil administration were secondary to the decrease in myocardial work and hence did not play a primary role in the drug's antianginal actions.

Our own detailed observations (Chew et al.[26]) support the work of Simonsen.[30] In our study, coronary and systemic hemodynamics were determined during continuous intravenous verapamil infusion; alterations in coronary vasomobility were assessed by a computer-assisted quantitative angiographic technique[25] that permitted the computation of cross-sectional areas of "normal" and stenotic segments of coronary arteries in addition to the calculation of stenosis flow resistance.[26] The mean data for systemic vascular resistance, coronary vascular resistance, and coronary sinus blood flow (as determined by continuous thermodilution) are shown in Figure 3. A typical computer printout of a 3-dimensional reconstruction of a coronary artery lesion plus its proximal and distal segments before and during verapamil infusion is presented in Figure 4. In these studies systemic and coronary vascular resistance decreased ($p < 0.01$) without a change in coronary sinus blood flow or myocardial oxygen consumption. Fifty % of the coronary lesions analyzed in both "normal" and stenosed areas dilated significantly with verapamil with a mean reduction in estimated stenosis flow resistance. However, these changes in coronary caliber were less striking when compared with those of nitroglycerin, which produced large vessel coronary vasodilation 2 to 3 times greater than did verapamil.

These observations indicate that in coronary artery disease, verapamil decreases systemic and coronary vascular resistance but exerts variable effects on coronary sinus blood flow and myocardial oxygen consumption. These data support the experimental work by Harder et al.[32] in which verapamil blocked calcium-dependent action potentials in both the large and small coronary vessels. However, compared with nitroglycerin, verapamil is only a mild epicardial coronary vasodilator; compared with dipyridamole, verapamil exerts only modest effects on coronary vascular resistance.[16,33] These relatively mild coronary vasodilator actions of verapamil in vessels not in spasm do not ne-

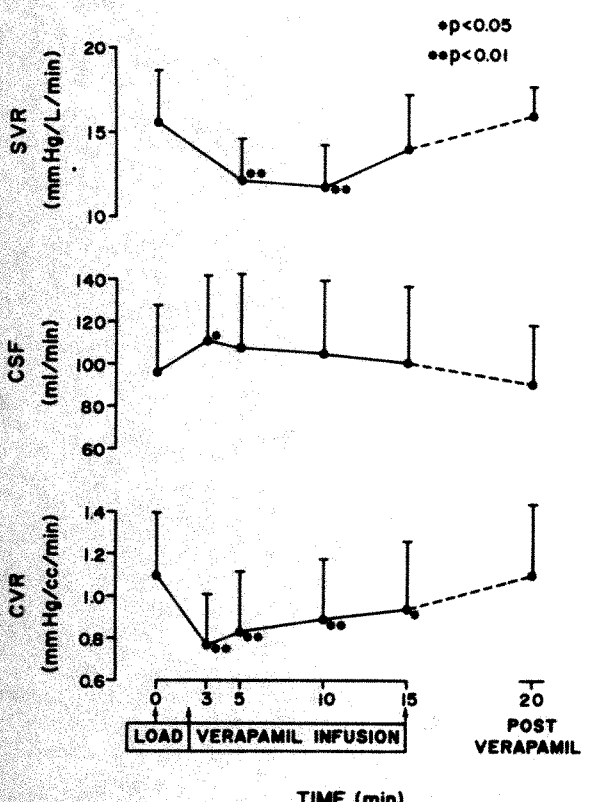

FIGURE 3. Effects of intravenous verapamil on systemic vascular resistance (SVR), coronary sinus flow (CSF), and coronary vascular resistance (CVR). The data presented are means ± standard deviation. Note that CVR and SVR decrease as CSF increases. These changes are consistent with the coronary vasodilator properties of verapamil. (Reproduced, with permission, from Chew et al. Clin Invest Med 1980;3:151–158.)

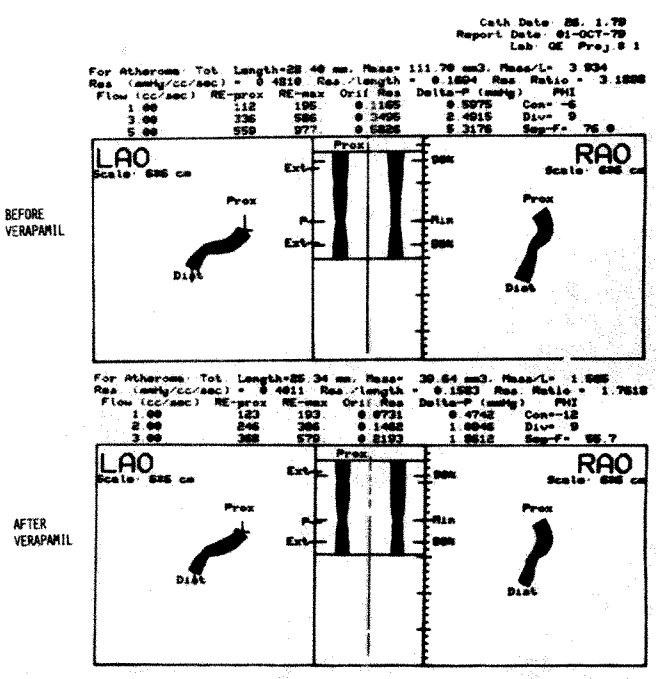

FIGURE 4. Computer printout of a coronary lesion analyzed before **(upper panel)** and after **(lower panel)** verapamil administration. LAO = left anterior oblique view; RAO = right anterior oblique view. Note the decrease in orifice resistance after verapamil consistent with the increase in vessel diameter at the site of maximal stenosis. (Reproduced, with permission, from Chew et al. Clin Invest Med 1980;3:151–158.)

gate the proven efficacy of verapamil in vasospastic angina.[34] Recent studies using quantitative coronary angiography show that intravenous verapamil significantly inhibits sympathetic-mediated and ergonovine-induced coronary vasoconstriction in diseased human coronary vessels to an extent that greatly exceeds its mild effects on such vessels in the basal state.[35] These data not only provide a rational basis for the use of verapamil in Prinzmetal's variant angina but also suggest that dilation of coronary stenosis may contribute to the drug's antianginal action when ischemia is produced consequent to a complex interaction between fixed obstruction and dynamic alterations in coronary artery caliber.[23]

Effects of verapamil in pacing-induced angina: The beneficial effects of verapamil on ischemic changes induced by incremental atrial pacing have been demonstrated in two independent studies. In 12 patients with coronary artery disease evaluated by Ferlinz and Turbow,[31] atrial pacing provoked anginal pain accompanied by S-T segment depression and a decrease in lactate extraction. After the administration of verapamil, repeat atrial pacing did not produce anginal pain in many patients and the time preceding angina was increased in the others; pacing-induced electrocardiographic and metabolic evidence of ischemia was also ameliorated. Using a similar protocol in 8 patients with coronary artery disease, Hecht et al.[15] noted that verapamil attenuated the magnitude of pacing-induced ischemic left ventricular dysfunction. Before verapamil, rapid pacing induced chest pain, a progressive decrease in left ventricular ejection fraction associated with new regional wall abnormalities, and a decline in myocardial lactate extraction (Fig. 5). When pacing was repeated during verapamil administration, atrial pacing to the same rate produced no or only minimal chest discomfort, did not decrease global or regional left ventricular ejection fraction, and did not alter lactate extraction (Fig. 5). Before verapamil, pacing-induced ischemia was accompanied by an increase in mean arterial (98.0 to 110.2 mm Hg) and pulmonary capillary wedge pressures (9.1 to 12.5 mm Hg); after verapamil, pacing did not alter systemic arterial or left ventricular filling pressures significantly (85.5 to 92.5 and 10.8 to 11.4 mm Hg, respectively).

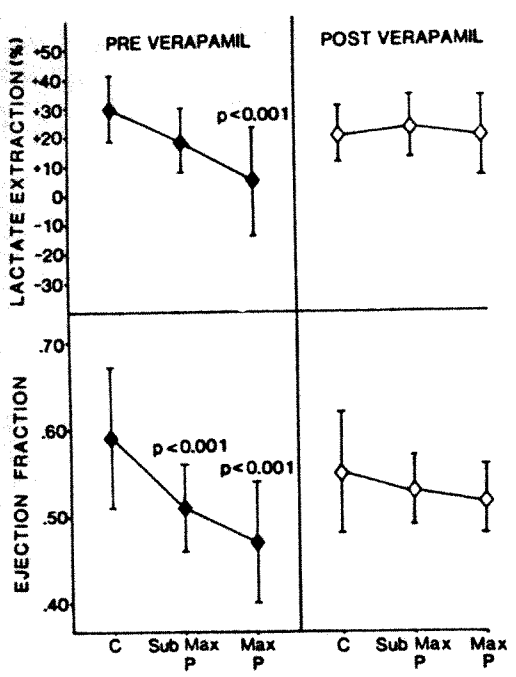

FIGURE 5. Changes in myocardial lactate extraction and left ventricular ejection fraction before and after verapamil infusion during coronary sinus pacing in patients with coronary artery disease. The data represent mean values ± standard deviation. Verapamil abolishes the abnormalities of lactate extraction and prevents the significant reduction of the ejection fraction at submaximal as well as maximal coronary sinus pacing. Max P = maximal pacing; Sub Max P = submaximal pacing. (Reproduced, with permission, from Hecht et al.[15])

The reduction in systemic arterial pressures and systemic vascular resistance that follows verapamil administration might be expected to reduce myocardial work and hence contribute to the antianginal effects of the drug. A *reduction* in myocardial oxygen consumption accompanied decreases in systemic pressure in the investigations of Ferlinz and Turbow,[31] who noted that verapamil *decreased* coronary sinus blood flow and did not alter coronary vascular resistance. This finding is in contrast to the mild coronary vasodilator effects without change in myocardial oxygen consumption noted after verapamil administration by Chew et al.,[26] Luebs et al.,[29] and Simonsen.[30] The reasons underlying the different results are unclear from the available data; however, verapamil likely exerts different effects on myocardial oxygen consumption and coronary sinus blood flow in different patients and in different clinical settings.

All these studies provide objective evidence for the antianginal actions of verapamil in coronary artery disease. The relative importance of the drug's effects on coronary vascular resistance and myocardial oxygen consumption in mediating these antianginal actions requires further study.

Effects of verapamil on myocardial performance during exercise: Josephson et al.[36] compared the effects of oral verapamil (480 mg/day) with those of oral propranolol (320 mg/day), each administered for 7 days, on the radionuclide global and regional left ventricular ejection fraction at rest and during supine bicycle exercise in 15 patients with coronary artery disease using a single-blind placebo cross-over protocol. Neither propranolol nor verapamil depressed the resting left ventricular ejection fraction, and both drugs were equally effective in preventing the exercise-induced decline in the left ventricular ejection fraction and in ameliorating exercise-induced electrocardiographic and segmental wall abnormalities (Fig. 6). Propranolol's beneficial effects were accompanied by marked attenuation of exercise-induced increases in heart rate (24.5%), systolic blood pressure (8.7%), and rate-pressure product (34.5%). Although verapamil therapy also decreased all 3 variables, the magnitude of its effect on heart rate (10.3%), systolic pressure (4.6%), and rate-pressure product (14.6%) was significantly less than that

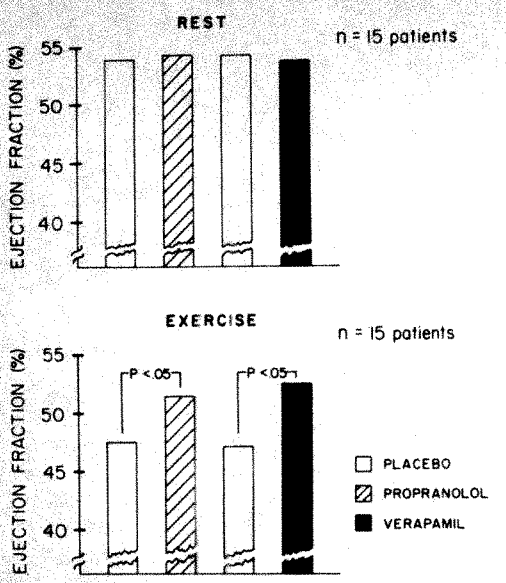

FIGURE 6. Comparative effects of verapamil and propranolol on left ventricular ejection fraction at rest and after supine bicycle exercise. Neither drug depressed resting left ventricular ejection fraction, and both prevented the decrease in ejection fraction that occurred on placebo during identical work loads. The data indicate that verapamil and propranolol have comparable antiischemic effects.

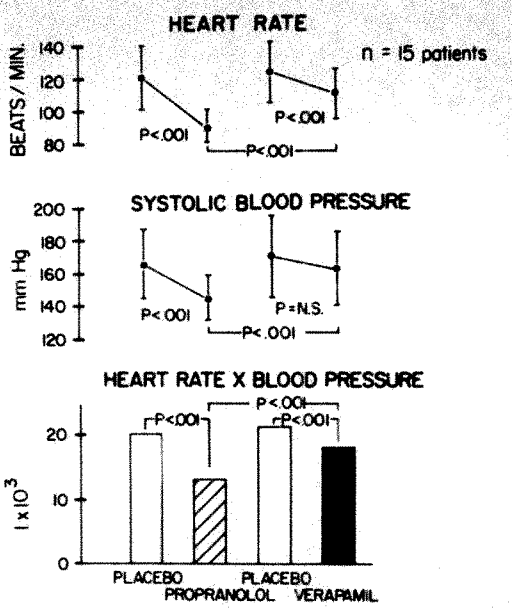

FIGURE 7. Comparative effects of orally administered propranolol and verapamil relative to that of a placebo on heart rate, blood pressure, and rate-pressure product during supine bicycle exercise in patients with coronary artery disease. Propranolol reduced rate-pressure product more than did verapamil at the identical exercise work load.

of propranolol (Fig. 7). Frishman et al.[37] and Johnson et al.[38] also noted that verapamil reduced the resting and exercise rate-pressure product significantly less than did propranolol despite comparable antianginal effects.

These data suggest that, although verapamil and propranolol exhibit comparable effectiveness in reducing the ischemic consequences of exercise stress in patients with coronary artery disease, the mechanisms underlying their beneficial effects probably differ significantly. The beneficial actions of propranolol and other beta-adrenergic blocking drugs appear to be primarily exerted by a decrease in myocardial oxygen requirements. However, verapamil exerts similar effects on myocardial ischemia while affecting the major determinants of oxygen consumption far less than does propranolol. Hence, a reduction in oxygen demand does not appear to be the sole mechanism involved in the antianginal effects of verapamil; decreases in coronary vascular resistance[26] and improvements in ventricular compliance[39] are likely to play additional and important roles.

Clinical Implications

The mechanisms underlying verapamil's antianginal effects are highly complex and likely involve the interaction of numerous circulatory responses. The drug is a mild dilator of epicardial coronary vessels but markedly attenuates sympathetically mediated and ergonovine-induced coronary vasoconstriction. These actions provide a rational basis for the drug's salutary effects in vasospastic ischemic syndromes in the presence or absence of coronary artery disease. The mechanisms underlying verapamil's beneficial actions in exertional angina are less clear. The drug attenuates the ischemic consequences of atrial pacing and of supine bicycle exercise in patients with angina pectoris; however, these changes are accompanied by minimal increases in coronary sinus blood flow and modest decreases in the principal determinants of myocardial oxygen consumption. Verapamil exerts antianginal benefits similar to those of propranolol, but indexes of myocardial oxygen consumption are reduced more strikingly by propranolol than by verapamil. Verapamil may exert its effects in exertional angina not only by decreasing myocardial oxygen consumption, but also by stenosis dilation and by improving ventricular compliance. These concepts provide a rational basis for the use of verapamil in patients with coronary artery disease regardless of whether ischemia results from primary (vasospastic) or secondary (stress-induced) mechanisms. Differences in the mechanisms underlying the antianginal actions of beta-antagonists and slow channel inhibitors suggest that additive effects might be obtained when these two classes of compounds are used in combination; preliminary studies have confirmed this important therapeutic possibility.[40]

Acknowledgment

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Verapamil and Digoxin: Their Respective Effects On Atrial Fibrillation and Their Interaction

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Although digitalis has long been used in the management of patients with atrial fibrillation (AF), it does not block the excessive increase in ventricular rate which occurs in such patients during mild exercise; in contrast, this inappropriate response is effectively blocked by verapamil. During regular sinus rhythm, the atrioventricular (A-V) node works well as a *delaying* structure (the P-R interval), and the ventricular rate is a function of the sinus rate only; however, in AF, the A-V node has to adopt the role of a *filter* for numerous wave fronts of activity, a function it fulfills poorly, especially during the enhanced sympathetic responses and decreased vagal tone that accompany exercise. In patients with AF, during exercise, these autonomic alterations override the vagal effects of digitalis on the A-V node, but verapamil remains effective by virtue of its direct action on the slow channel ionic fluxes within the A-V nodal cells. The beneficial effect of verapamil on ventricular rate is accompanied by a significant improvement in maximal exercise capacity in patients with AF receiving long-term oral verapamil therapy; thus, it appears superior to digoxin in the treatment of chronic AF.

Verapamil significantly increases serum digoxin concentration by reducing renal and nonrenal digoxin clearance and, possibly, by reducing its volume of distribution. Serum digoxin concentrations also are increased by nifedipine. The clinical implications of these interactions are unclear; at present it is recommended that the dose of digoxin be reduced when therapy with a calcium antagonist is given concomitantly.

About digitalis in atrial fibrillation: "Although it is usually possible to control the rate . . . at rest or quietly exercising, it is rarely possible to control the rates adequately in conditions of freer exercise."

Sir Thomas Lewis, 1934[1]

About verapamil in atrial fibrillation: ". . . Verapamil is the most effective and probably the safest drug for effecting a conduction delay or block within the A-V node."

L. Schamroth, 1980[2]

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Although much attention has been given to the use of verapamil in the acute management of supraventricular tachyarrhythmias,[3–6] there are comparatively few data concerning its usefulness in the long-term treatment of these arrhythmias. This article reviews the use of verapamil in the long-term control of excessive ventricular rates in patients with atrial fibrillation. The interaction of verapamil and digoxin is also discussed.

Effects of Digitalis and Verapamil in Atrial Fibrillation

Digitalis in the Management of Atrial Fibrillation

Historical perspectives: 80 years of digitalis therapy: The two foregoing quotations highlight the evolution that is gradually taking place in the treatment of patients with AF. MacKenzie[7] first demonstrated that digitalis slows the ventricular rate in patients with AF; however, he administered the drug to patients with congestive heart failure, so that the decrease in heart

rate may have been related in part to the improvement in cardiac performance that follows digitalis therapy rather than to the direct effects of the drug on atrioventricular (A-V) conduction. Nevertheless, digitalis became the keystone of the treatment of both acute and chronic AF and remained so for nearly 80 years, in spite of the observations of Sir Thomas Lewis.[1] However, Blumgart[8] and others[9–18] showed that although digitalis slowed the ventricular rate at *rest* in patients with AF, it failed to do so during exercise. In the words of Gold et al.[12]: "In general, our experience is that as a group patients with auricular fibrillation without heart failure are rather more resistant to slowing by digitalis."

Other investigators have defended the role of digitalis in the management of patients with AF. Modell et al.[19] advocated the use of incremental doses of the drug followed by testing for adequacy of dosage by determining the increase in heart rate after atropine. Redfors[20–22] reported that digoxin attenuated exercise-induced tachycardia in patients with AF; however, the decrease was small (13%), even when the dose and plasma concentration of digoxin were doubled.

Controlled clinical trials of digitalis in AF: We recently reinvestigated the response of patients with AF to digitalis in two separate studies. In the first, the ventricular response at rest and during exercise was evaluated in 23 patients with chronic AF during treatment with their usual dose of digoxin (0.25 to 0.50 mg daily) and again after we raised the daily digoxin dose so as to triple serum digoxin concentrations (0.6 to 1.8 ng/ml). We noted that increases in the dose of digoxin failed to decrease the ventricular rate at rest or during mild exercise (450 kiloponds per minute [kpm] for 2 minutes) significantly more than did the lower dose of digoxin.[23] Whether low doses of digitalis were beneficial was not determined because patients were not evaluated while receiving no therapy.

In the second study, 24 patients with chronic atrial fibrillation without congestive heart failure were evaluated as part of a comparative trial of digitalis and verapamil.[24] Ventricular rates were assessed at rest and during mild exercise (300 kpm for 3 minutes) *before and after* the administration of digoxin, administered in 2 different daily oral doses, 0.25 mg and 0.50 mg daily, and in randomized order. Chronic oral digoxin therapy produced moderate decreases in the ventricular response at rest (108 beats/min on no therapy, 95 beats/min on digoxin 0.25 mg daily, and 88 beats/min with 0.5 mg daily), but exerted minimal effects during exercise (160 beats/min on no therapy, 155 beats/min with digoxin 0.25 mg daily, and 148 beats/min with digoxin 0.50 mg daily), despite a mean serum digoxin concentration of 1.71 mg/ml achieved with a daily dose of 0.5 mg (Fig. 1).[24] The excessive ventricular response during mild exercise (300 kpm for 3 minutes) was similar during all three treatment periods; the mean heart rate with 0.5 mg digoxin was reduced only by 8%, which, although significantly less ($p < 0.025$) than the untreated response, remained out of proportion to the minimal exercise performed.

Thus, digoxin has major limitations in the long-term management of patients with AF. To understand the reasons for the failure of digoxin therapy, a brief review of the physiology of atrioventricular conduction in AF is necessary.

A-V Node in AF

The irregularity and apparent randomness of the ventricular rate in AF is the ultimate outcome of a complex interplay of several factors, which can be grouped into three major categories: (1) the nature of the electrical input into the A-V node, that is, the number, irregularity, and direction of atrial impulses that bombard the approaches to the A-V node; (2) the responsiveness of A-V nodal cells and the preservation of intranodal conduction; and (3) the modulation of both (1) and (2) by extracardiac factors such as sympathetic and parasympathetic influences and the effects of drugs.

Atrial electrical input: In AF, most of the 400 to 800 impulses that bombard the approaches to the A-V node are blocked at the atrionodal junction or in the upper part of the A-V node. The ability of the remaining impulses to excite the successive layers of A-V nodal cells and traverse the entire A-V node is predicted upon the organization and direction of the excitatory wave front.[25,26] An increase in vagal tone or the institution of digitalis therapy could decrease the ventricular rate not only by their well-established effects on intranodal conduction, but also by increasing the electrical input to the A-V node at this point. By decreasing the atrial refractory period and increasing atrial conduction velocity, acetylcholine and digitalis may increase the number of, and thereby the disorganization of, the atrial impulses that invade the upper part of the A-V node[27–31]; this reduces the ability of these impulses to traverse the A-V node. Verapamil also may increase the atrial rate in some patients with AF[32] and thus could exert a similar negative influence on the organization of the excitatory wave fronts.

A-V nodal transmission of impulses: Propagation of the excitatory wave front across the A-V node takes place with a relatively low margin of safety. The anatomic nature and arrangement of the A-V nodal fibers, their dependence on ionic transfer across "slow channels" for activation, and their time-dependent recovery from refractoriness are responsible for the relative ease with which impulses are delayed or blocked within the A-V node, especially at high and irregular rates.[25,33–36] Decremental conduction[25,36] and inhomogeneity of propagation[25] also may affect the propagation of subsequent atrial impulses by setting up various degrees of inexcitability in successive layers of cells of the A-V node,[35–41] an effect called "concealed conduction" by Langendorf.[38]

Modulating factors: autonomic influence and drugs: The complex events that result in the apparently random ventricular response to AF are strongly influenced by autonomic nervous system activity. Ace-

tylcholine markedly impairs A-V conduction, both by depressing the amplitude and rate of rise of the action potentials in the middle region of the A-V node and by reducing the effectiveness of the upper nodal cell potentials as a stimulus for the middle region.[33,42,43] Catecholamines markedly enhance A-V conduction by increasing the rate of depolarization and overshoot of the action potential of the upper and middle nodal cells.[44] At rest, vagal and sympathetic tone are evenly balanced[45,46]; hence, the ventricular rate usually oscillates within limited boundaries. However, any stimulus such as stress or exertion which leads to either an increase in adrenergic or a decrease in vagal influences will markedly enhance the A-V transmission of atrial impulses. This fact creates a serious problem for the patient with AF.

In normal sinus rhythm, the A-V node acts only as a *delaying* structure (the P-R interval). Sympathetic enhancement of A-V conduction does not per se affect heart rate, since the ventricular rate is a priori determined by the firing frequency of the sinoatrial node (S-A) only, and the latter increases in a manner commensurate with the intensity of sympathetic influences. Therefore, the ventricular rate is directly related to the effect of stress on the firing frequency of the S-A node and is not affected by autonomic-induced changes in A-V nodal conduction. In AF, where the A-V node is constantly bombarded by 600 impulses every minute, A-V nodal conductivity becomes the only regulating mechanism capable of controlling the ventricular rate. Although the A-V node functions well as a *delaying* structure, it is not effective as a *filter* of excessive atrial activity, especially in the presence of the increased sympathetic and decreased vagal tone associated with stress and exercise. Enhanced A-V nodal conduction in these conditions, therefore, results in excessive impulse transmission and disproportionately high ventricular rates, far beyond the "normal" and expected acceleration produced by similar stress in the presence of sinoatrial rhythm.

Digitalis slows conduction across the A-V junction and prolongs the effective refractory period at concentrations that do not otherwise modify the nodal action potential.[47] This change is the result of the cholinergic and antiadrenergic actions of digitalis[48] and is greatly attenuated by the vagolytic action of atropine or by exercise.[49] Although studies in transplanted denervated human hearts indicate that digitalis may exert direct actions on A-V conduction,[50] these actions appear small in magnitude compared with the role of the autonomic nervous system in mediating the drug's effects.[48,50,51] This explains the minimal effect of digitalis on the ventricular response in AF during stress and exertion, states accompanied by a withdrawal of vagal tone and by a marked increase in adrenergic activity[46]; these forces serve to abolish the indirect effects of digitalis and override whatever direct actions the drug may exert on the A-V junction. The inevitable result is a marked increase in the number of impulses conducted through the A-V junction.[52]

Verapamil in the Management of AF

Mechanism of action of verapamil: In addition to its possible effects on atrial impulses, verapamil depresses the amplitude of action potentials in the upper and middle regions of A-V node and lengthens the time-dependent A-V nodal refractory period[53–56]; the drug's actions on the amplitude of middle A-V nodal action potentials are *more* pronounced at rapid than at slow atrial stimulation rates.[53] These effects of verapamil are due to its *direct* blocking properties on the slow ionic channels of the A-V node[53–56] and are not mediated by the cholinergic or adrenergic nervous systems.[54–57] Thus, verapamil (but not digitalis) continues to exert its direct effects during exercise.

Intravenous verapamil in AF: The blocking properties of verapamil on the *human* A-V node in atrial fibrillation were first discovered in 1965 by Bender et al.[58] In 156 cases of AF, these investigators achieved a 24% decrease in the mean ventricular rate with a 5 to 15 mg dose of intravenous verapamil.[59] Numerous reports subsequently confirmed the prompt, effective, and relatively safe control of the ventricular rate with intravenous verapamil in patients with acute and chronic AF of various causes, including that associated with acute myocardial infarction.[60–72]

The acute effects of verapamil are particularly important in the *fully digitalized* patient with uncontrolled AF, to whom the administration of additional doses of digoxin is avoided because of fears of digitalis toxicity. Not all patients respond to verapamil, however. Schamroth[73] observed significant slowing of the ventricular rate in 78% of 1,474 episodes of AF; the faster the rate before therapy, the greater the reduction in rate after administration of verapamil. The observation that the magnitude of the response depends on the rapidity of the pretreatment ventricular rate is similar to the experimental findings of Wit and Cranefield[53] in the A-V node of the rabbit. Patients with very high ventricular rates associated with acute congestive heart failure, however, may not respond even to high doses (and plasma levels) of verapamil.[70]

AF in the Wolff-Parkinson-White syndrome: In this entity, atrial impulses may be propagated to the ventricles through the A-V node, through the accessory pathway, or by both mechanisms. Since verapamil has little effect on the fast sodium channels, it has little effect on the accessory pathway itself,[74] since the latter is composed of ordinary myocardial cells; however, verapamil may accelerate the ventricular response in patients with AF associated with preexcitation syndromes by a variety of mechanisms.[69,71,74] Verapamil can shorten the refractory period of the accessory pathway in some patients[74]; furthermore, the increased block at the A-V node induced by the drug may enhance antegrade conduction through the accessory pathway indirectly by decreasing the number of available abortive impulses attempting to pass retrogradely through the accessory pathway[69,71]; this also may occur with digitalis.[75] Lastly, the increased sympathetic tone resulting from the decrease in systemic vascular resistance

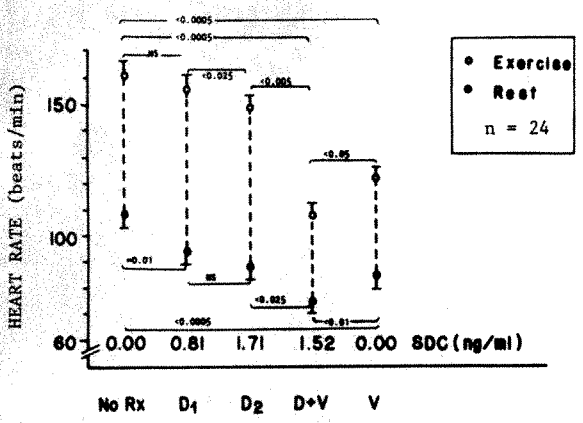

FIGURE 1. Ventricular rate of 24 patients with chronic atrial fibrillation at rest and after mild exercise (300 kpm for 3 minutes) before therapy (No Rx); during treatment with digoxin, 0.25 mg daily (D_1) or 0.50 mg daily (D_2); during combined therapy of digoxin, 0.25 mg, and verapamil, 240 mg daily (D + V); and during treatment with verapamil, 240 mg daily (V). The p value was <0.001 for the entire comparison analyzed by one-way analysis of variance for multiple comparisons; p values are also shown for comparison among treatment phases. SDC = mean serum digoxin concentration during each treatment.

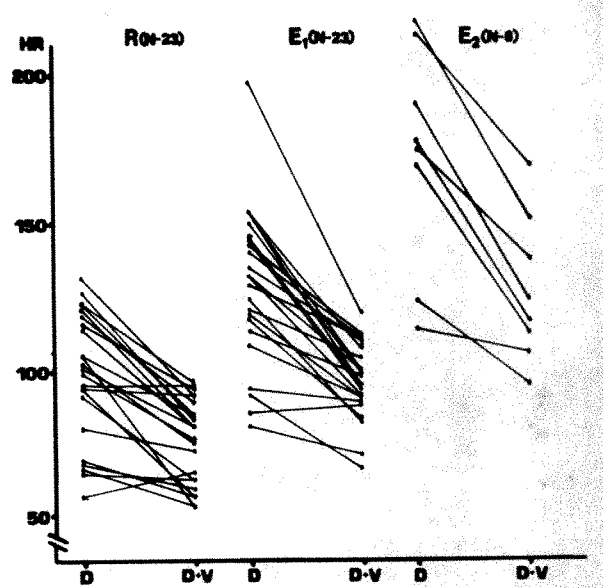

FIGURE 2. Heart rate of 23 digitalized patients with chronic atrial fibrillation before and after the addition of 160 to 240 mg of verapamil daily; ventricular responses were assessed at rest, during mild exercise (E_1: 300 kpm for 3 minutes), and in 8 patients after moderate exercise (E_2: an additional 3 minutes at 600 kpm). D = digoxin therapy only; D + V = digoxin combined with verapamil. (Adapted from Reference 78, with permission.)

after intravenous administration of verapamil could facilitate the transmission of impulses across the accessory pathway.[71] Petri et al.[76] recently showed that verapamil decreased the ventricular rate in patients with the Wolff-Parkinson-White syndrome if most of the impulses were propagated across the A-V node, whereas it *increased* the ventricular response if most of the impulses were conducted across the accessory pathway; however, the number of beats conducted via the accessory pathway was increased after the administration of verapamil in *both* groups of patients. Verapamil is not recommended to control the ventricular rate in patients with AF associated with preexcitation syndromes, in whom conduction occurs primarily by the accessory pathway.

Effectiveness of oral verapamil in AF: Although early doubts were expressed concerning the efficacy of *oral* verapamil in patients with supraventricular tachycardia and AF,[59,62,77] these fears have proved unfounded, if sufficiently large doses of the drug were administered to overcome the extensive hepatic metabolism of the drug. We conducted a series of clinical investigations to evaluate the role of oral verapamil (either alone or in combination with digitalis) in the management of patients with chronic AF.[24,78,79] In the first study, the ventricular response at rest and during two levels of exercise was evaluated in 23 digitalized patients with chronic AF before and after the addition of 160 to 240 mg of verapamil daily. Mean resting heart rate decreased from 99 ± 23 (mean ± standard deviation) to 76 ± 15 beats/min (p <0.001) after the addition of verapamil; the drug also reduced heart rate during mild exercise (300 kpm for 3 minutes) from 128 ± 24 to 96 ± 13 beats/min (p <0.001), and during moderate exercise (600 kpm for 3 minutes) from 173 ± 38 to 127 ± 20 beats/min (p <0.01) (Fig. 2).[78] In a fashion similar to that of previous investigators,[53,73] the effect of oral verapamil on the resting ventricular rate was more marked in the patients with higher pretreatment heart rates than those with lower rates of response.

Following the encouraging results obtained with the combination of verapamil and digoxin, we investigated the effectiveness of verapamil as the *only* therapeutic agent in chronic AF.[24] We compared the ventricular responses at rest and during exercise in 24 patients with chronic AF during five treatment periods: (1) on no treatment, (2) on oral verapamil *alone* (240 mg daily), (3) and (4) on two dose levels of digoxin therapy (0.25 and 0.5 mg daily), and (5) on the combination of digoxin 0.25 mg daily plus verapamil (240 mg daily). As discussed earlier, digoxin was ineffective in controlling the ventricular rate during exercise; in contrast, verapamil *alone* markedly decreased (by 24%) the ventricular response both at rest and during exercise when compared with no treatment (p <0.0005) (Fig. 1). The combination of verapamil and digoxin was more effective than verapamil alone (a reduction in exercise response by 29%), but the magnitude of the additional benefit with the addition of digitalis was small.

Finally, it is important to prove that the reduction in ventricular rate in AF is clinically beneficial.[80] Although therapy with beta-blocking agents causes a marked reduction in the ventricular response at rest and during exercise,[23,81] exercise capacity *deteriorates* in patients treated with propranolol.[81] To determine whether verapamil might produce similar detrimental effects, we evaluated maximal exercise capacity using a multi-

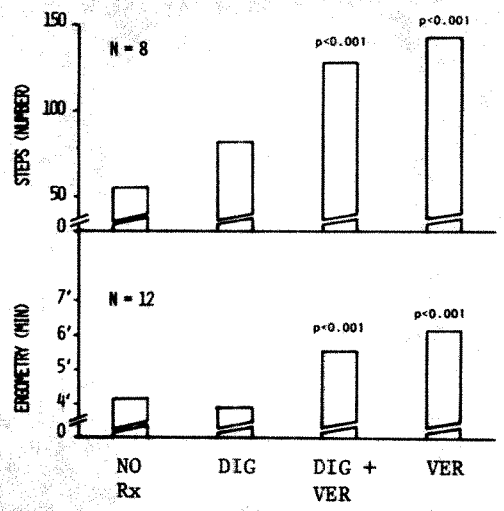

FIGURE 3. Maximal exercise capacity assessed by number of steps on a modified Master test and by the maximal duration of time spent in minutes in a single stage ergometry test in 20 patients with chronic atrial fibrillation receiving either no treatment (NO Rx); digoxin, 0.25 mg alone (DIG); digoxin combined with verapamil (DIG + VER); or verapamil alone (VER).

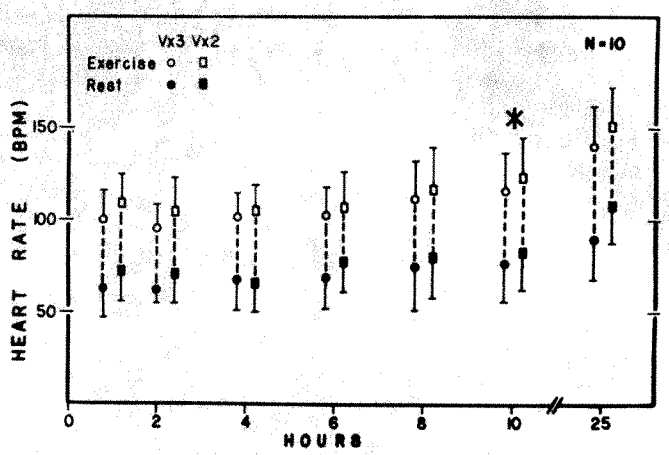

FIGURE 4. Comparison of efficacy of verapamil 80 mg in three daily doses (V × 3) versus 80 mg in two daily doses (V × 2) in 10 digitalized patients with chronic atrial fibrillation. On the day of testing, the patients took their usual morning dose of verapamil only, and the ventricular rate was determined every 1 or 2 hours thereafter, at rest and after a standardized submaximal exercise test. Heart rate remained controlled for more than 8 hours after the administration of verapamil. Ten and 25 hours later there was a significant increase in heart rate, but this occurred similarly with both regimens. The **asterisk** shows the hour in which the increases in rate with both regimens became statistically significant ($p < 0.05$).

stage ergometry exercise protocol in a double-blind, randomized crossover study of 20 patients with chronic AF treated with digitalis.[79] Maximal exercise capacity was scored according to a work capacity formula, where the duration of each stage of exercise was multiplied by the work performed. When the combination of digoxin and verapamil was compared with digoxin alone, maximal exercise capacity was increased 54% by the addition of verapamil (from 522 ± 258 to 806 ± 349 units, $p < 0.001$), while heart rate and systolic blood pressure at the point of maximal exercise were significantly decreased (from 165 ± 28 to 136 ± 29 beats/min, $p < 0.001$, and from 161 ± 89 to 153 ± 86 mm Hg, $p < 0.01$, respectively). In a second group of 20 patients, we compared the maximal number of steps achieved in a modified Master one-step test and the maximal duration of 300 kpm ergometry during no treatment, during treatment with digoxin 0.25 mg daily, verapamil alone (240 mg daily), and a combination of both drugs. The superior control of resting and exercise heart rate with verapamil was associated with improved effort tolerance; the addition of digoxin to verapamil did not produce significant additional benefits compared with those seen with verapamil alone (Fig. 3).

The patients in our studies have either felt better or unchanged after the institution of verapamil therapy. No serious adverse effects were detected with the doses used. All patients with AF had long-term control of ventricular rates (up to 5 years) similar to that seen during the initial treatment period.

Accordingly, we believe that verapamil is now the treatment of first choice in the management of patients with chronic AF; the doses used range from 160 to 240 mg daily, with the dose titrated according to the results of low level (300 kpm) ergometry. Digitalis therapy is reserved for patients who require and may benefit from its potential inotropic effects. The dosage of verapamil may have to be adjusted periodically. For example, the evening dose may be omitted in many patients (conversion of 80 mg three times daily to 80 mg twice daily) without a loss of effective rate control (Fig. 4); this adjustment may avoid excessive nocturnal bradycardia. If the rate appears to escape the influence of verapamil,[71] the development of congestive heart failure should be suspected, because heart failure tends to increase the ventricular rate even during therapy with the drug.[70] Although the ventricular response in patients with AF frequently may be regularized by increasing the dose of verapamil,[82] we do not attempt to achieve this effect because a regularized response has not been shown to provide any greater benefit than that achieved by rate control, and the increase in dose is likely to be associated with increased drug toxicity.

Plasma verapamil concentrations: Both intravenous and oral verapamil administration produce a wide range of plasma verapamil concentrations in patients with and without tachyarrhythmia.[70,83,84] Nevertheless, the prolongation of A-V conduction with therapeutic doses of verapamil is dependent on the plasma drug levels achieved in each patient.[85,86] Sung et al.[87] related the time course of plasma verapamil concentrations and its therapeutic effects in two groups of patients, one with inducible supraventricular tachycardia and the other with AF and a rapid ventricular response. Peak levels of verapamil blocked the induction of supraventricular tachycardia and slowed the ventricular response in AF; however, tachycardias could be induced once again 30

to 45 minutes after verapamil administration, when the plasma levels of the drug had decreased to 50% of their peak values. In contrast, slowing of the ventricular rate in the patients with AF lasted much longer (2 to 3 hours), at which time plasma levels of the drug were less than 20% of their peak value. Hence, interruption of a tachycardia circuit and prevention of tachycardia induction appears to require higher verapamil plasma concentrations than does slowing of A-V conduction in AF.

Our results with oral verapamil confirm the observations of Sung et al.[87] We related plasma concentrations of the drug to the rapidity of the ventricular response with chronic AF in 10 patients who received 80 mg of verapamil twice daily. The maximal decrease in ventricular response was observed at peak plasma drug levels (158 ± 83 ng/ml), but heart rate was still effectively controlled 8 hours after drug administration, when plasma concentrations had declined to 62 ± 28 ng/ml, a concentration substantially below the effective drug concentration for preventing the induction of supraventricular tachycardia.[83]

The role of plasma verapamil determinations in the clinical management of AF is unclear. Dominic et al.[70] found a poor correlation between rate response and plasma drug levels. Other factors, such as high circulating catecholamines, drug interactions, the degree of binding of verapamil by the A-V node, and the presence of biologically active metabolites are likely to influence the pharmacodynamic actions of verapamil in AF; all these factors likely account for the poor relationship between plasma drug levels and response. The finding of a low plasma verapamil level in a patient with apparently refractory AF or, vice versa, a very high plasma concentration in a patient with a profound reduction in ventricular rate is likely to be helpful in determining the optimal dose of verapamil to be used.

Interaction of Digitalis and Verapamil

Effects of Verapamil on Serum Digoxin Concentrations

Several drugs have recently been shown to influence the metabolism and disposition of digoxin,[88–91] but most have not proved important clinically. The first evidence that digoxin drug interactions were clinically relevant was provided by reports that quinidine increased serum digoxin concentration and could cause digitalis toxicity.[92–95] These reports suggested the possibility that a similar interaction might be occurring with digoxin and verapamil in patients receiving both drugs for chronic AF.

We conducted two studies to investigate a possible interaction. In the first, serum digoxin concentrations were determined in 49 patients with chronic AF receiving a daily dose of 0.25 mg of digoxin before and 2 weeks after the addition of oral verapamil, 240 mg daily.[96] Verapamil increased the mean serum digoxin concentration by 70% (from 0.76 ± 0.35 to 1.31 ± 0.54 ng/ml, p <0.0005). Verapamil also increased the serum digoxin concentration in 5 patients with atrial fibrillation receiving 0.50 mg daily of digoxin (from 1.39 ± 0.46 to 2.51 ± 0.80 ng/ml, p <0.05).[96] In the second study, which was conducted as part of the double-blind crossover evaluation of verapamil on exercise capacity in 29 patients,[79] mean serum digoxin concentrations rose by 65% after the addition of verapamil. Similar increases in serum digoxin concentration after the addition of verapamil have been observed by others.[97,98]

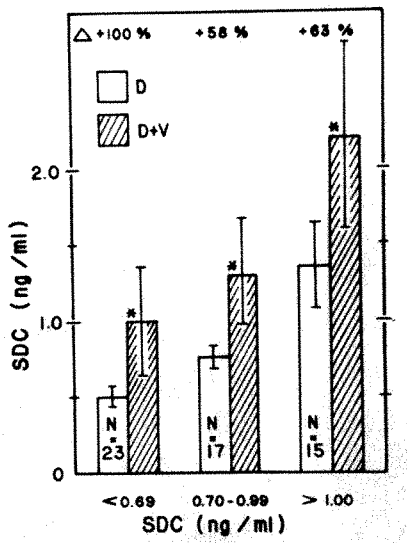

FIGURE 5. The mean serum digoxin concentration (SDC) before and after the addition of verapamil on the **ordinate**, plotted against the original mean serum digoxin concentration during treatment with digoxin alone on the **abscissa.** SDC increased uniformly in all 3 subgroups of patients. Δ% = percent change in serum digoxin concentration. N = number of patients in each subgroup. **Lines** represent 1 standard deviation. **Asterisks** indicate p <0.05.

Our original study[96] demonstrated the additional following characteristics of the digoxin-verapamil interaction: (1) It occurs at all levels of digitalization (Fig. 5). (2) It is time-dependent; the serum digoxin concentration increases gradually and linearly during the first few days of verapamil therapy, reaches 90% of the peak values by 7 days, and peak values by 14 days. (3) It is dose-dependent; the serum digoxin concentration is increased more by 240 mg daily of verapamil than by 160 mg daily of the drug (0.60 ± 0.11 ng/ml before verapamil, 0.84 ± 0.18 with 160 mg of verapamil daily, and 1.24 ± 0.4 ng/ml with 240 mg of verapamil daily, p <0.01). (4) The serum digoxin concentration remains elevated throughout the day, and thus truly represents a new steady state induced by verapamil.

Mechanisms Underlying the Interaction of Digoxin and Verapamil

To define the mechanisms by which verapamil increases serum digoxin concentration, we determined renal digoxin clearance before and during therapy with verapamil in 3 normal volunteers and 7 patients with AF.[96] Renal clearance fell by 40 to 53%, while the serum digoxin concentration rose by about 40% (Fig. 6); one

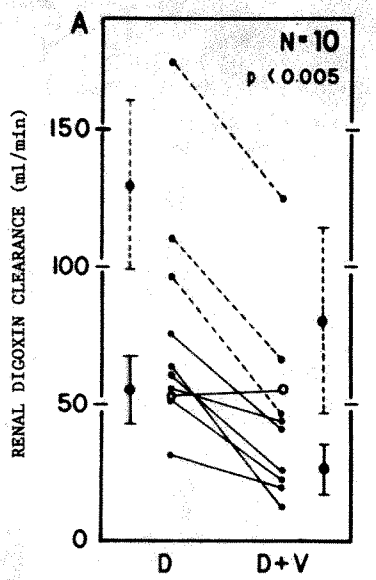

FIGURE 6. Individual and mean renal digoxin clearance in 7 patients with chronic atrial fibrillation (**solid lines**) and 3 normal volunteers (**dashed lines**). Digoxin clearance decreased from 55 ± 12 to 26 ± 10 ml/min ($p < 0.005$) in 6 patients and remained unchanged in the single patient (shown by the **open circles**) in whom serum digoxin concentration failed to increase. Digoxin clearance also decreased from 129 ± 33 to 79 ± 35 ml/min ($p < 0.005$) in the 3 normal volunteers. D = digoxin; D + V = digoxin and verapamil. (Adapted from Reference 96, with permission.)

patient had no significant change in either serum digoxin concentration or renal digoxin clearance. Thus, the increase in serum digoxin concentration can be explained in part by a decrease in renal clearance of the drug. Since glomerular filtration was not affected by verapamil in these 10 patients, the decrease in renal clearance of digoxin is likely due to a decreased tubular secretion of the drug, an effect similar to that described by quinidine.[95] Other investigators recently showed that both the metabolic (nonrenal) clearance and the volume of distribution of digoxin is decreased by verapamil, in addition to the decrease in renal digoxin clearance.[84,98]

The ultimate biochemical mechanism and sites of action of the interaction remains to be clarified. Nifedipine also increases serum digoxin concentration,[97] suggesting that the renal tubular secretion of digoxin may be mediated by slow channel-dependent mechanisms.

Clinical Implications

The clinical implications of the interaction between verapamil and digoxin are unclear. By increasing the availability of digoxin to brain or cardiac tissue, verapamil could theoretically provoke digitalis toxicity, in a fashion similar to quinidine.[99,100] Verapamil could either detract from the positive inotropic effect of digoxin by displacing digoxin from cardiac binding sites (as has also been suggested for quinidine),[101,102] or may enhance its inotropic effect by increasing circulating drug levels.[103] Of our original 49 patients,[96] 7 (14%) had symptoms and electrocardiographic findings compatible with mild to moderate digitalis intoxication, and serum digoxin concentrations exceeded 1.9 ng/ml in 5 of these 7 patients. In the 6th patient, the plasma level of digoxin was only 1.4 ng/ml, but this was measured 60 hours after the last dose of digoxin. In the seventh patient, A-V junctional rhythm was present with a serum digoxin concentration of 0.88 ng/ml; this probably represented the additive effects of digoxin and verapamil rather than an effect mediated by an increase in serum concentration of digoxin. In our second study of 29 patients, only one patient (3.4%) had serious digitalis toxicity.

Based on our observations, we estimate the risk of developing digitalis toxicity in a large population receiving 240 mg daily of verapamil at approximately 10%. This percentage could be higher if larger doses of verapamil are used. Whether verapamil increases or decreases the inotropic effects of digoxin on the heart, however, remains unclear.

The interaction between verapamil and digoxin does not mitigate against the use of both drugs in combination. Most patients with normal renal function receiving 0.25 mg of digoxin daily are underdigitalized, and thus the interaction may actually result in more adequate digitalization. In view of the low toxic to therapeutic ratio of digoxin, it is evident that caution should be exercised when verapamil is administered to fully digitalized patients. Until further studies are completed, we recommend decreasing the dose of digoxin by one third to one half, followed by determination of the serum digoxin concentration at appropriate intervals. The problem is simplified in the patient with AF because the ventricular response may serve as an adequate indicator of the efficacy of the combined use of digoxin and verapamil.

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Hemodynamic and Clinical Effects of Combined Verapamil And Propranolol Therapy in Angina Pectoris

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Because of their common negative chronotropic and inotropic effects, combined therapy of beta-adrenergic blocking drugs and calcium channel antagonists has long been feared to produce synergistic cardiodepressant effects. To evaluate whether such fears are justified when such therapy is used in patients with angina pectoris, five hemodynamic and clinical studies were reviewed. These studies indicated that in patients with preserved ventricular function treated with low or moderate doses of propranolol, verapamil produced little change in cardiac performance; this finding was not significantly different from the effects of verapamil in the absence of beta-blockade. In patients receiving large doses of propranolol, verapamil produced modest but significant cardiodepressant effects; these could be avoided by withdrawal of propranolol for 24 hours. Adverse reactions, when they occurred, were primarily hemodynamic rather than electrophysiologic.

Short-term (48 hours) and long-term (4 weeks) randomized controlled trials, which objectively evaluated exercise tolerance in patients with angina pectoris, demonstrated that combined therapy of verapamil and propranolol was superior not only to placebo but also to either drug alone. In patients with preserved left ventricular function, the incidence of adverse effects with combined therapy was small (less than 10%) but increased to 25% in patients with poor left ventricular performance (ejection fraction less than 30%). Combined therapy of nifedipine and propranolol also produced adverse hemodynamic and clinical reactions.

Combined therapy of beta-adrenergic and calcium channel antagonists can provide substantial clinical benefits for patients with angina pectoris who remain symptomatic with either agent used alone. Because adverse effects can occur, however, patients being considered for such treatment need to be carefully selected and observed.

Verapamil is of established value in the treatment of a wide variety of cardiovascular disorders.[1–4] By inhibiting slow channel activity and thereby blocking the entry of calcium into cardiac muscle cells, the drug exerts direct negative inotropic and chronotropic effects and slows atrioventricular conduction in isolated heart preparations.[5,6] Beta-adrenergic receptor antagonists produce similar hemodynamic effects, possibly because of interference with *intra*cellular calcium transport across the sarcoplasmic reticulum.[7,8] Therefore, it is not surprising that investigators have long suspected that additive cardiodepressant effects might accompany combined therapy with these two drugs because of their ability to inhibit, by different mechanisms, calcium transport to active sites within cardiac contractile elements.[9,10]

Early pharmacologic studies in dogs confirmed the existence of a cardiocirculatory interaction between verapamil and beta-adrenergic antagonists.[11–13] When verapamil alone was administered in these canine experiments, the drug produced marked peripheral vasodilation by its inhibition of calcium influx in vascular smooth muscle; the decrease in peripheral resistance stimulated reflex increases in heart rate and cardiac output, despite direct negative inotropic actions of the drug on the myocardium. In contrast, when verapamil was readministered to dogs after pretreat-

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ment with propranolol, cardiac output and heart rate failed to increase; furthermore, significant decreases in myocardial contractile force and increases in ventricular filling pressures were frequently observed.[11–13]

Because of the similar cardiovascular effects and the hemodynamic interactions noted in animal studies, combined verapamil and propranolol therapy has been feared to produce adverse clinical reactions in patients with heart disease.[9] These concerns were supported by clinical case reports of hypotension, atrioventricular block, and asystole after the administration of verapamil to patients receiving beta-adrenergic blocking drugs.[9,14–22] These events were largely observed, however, after the administration of verapamil intravenously to acutely ill patients with supraventricular tachyarrhythmias, many of whom also had congestive heart failure. Severe hypotension, heart block, and asystole have not been reported during combined therapy in patients with coronary artery disease receiving verapamil for angina pectoris. Furthermore, although the immediacy of reported episodes of hypotension, heart block, and asystole to the administration of intravenous verapamil left little doubt as to the causative role of calcium channel blockade in these adverse reactions, the importance of concomitant therapy with beta-adrenergic antagonists was unclear, because similar adverse events can occur after the administration of verapamil alone.[9,17,23–27]

To establish the nature and clinical relevance of the interaction between verapamil and beta-adrenergic antagonists in patients with nondysrhythmic disorders, we reviewed a series of clinical investigations to determine the clinical utility and safety of combined therapy in such patients.

Effects of Verapamil in the Absence of Beta-Blockade

The hemodynamic responses to verapamil are the net result of two interacting forces: its direct negative inotropic and chronotropic effects and its peripheral vasodilator actions[28,29]; the latter not only reduce ventricular afterload,[30] but also stimulate beta-adrenergic reflexes,[12,28,29,31] both of which serve to counteract the direct cardiodepressant effects of the drug. Therefore, the responses to verapamil are determined by the dose of verapamil administered (because the depressant effects of the drug are dose-dependent[6,11,12,29,32]) and the integrity of beta-adrenergic reflex responses. With small doses of verapamil, increases in cardiac output and heart rate occur regularly in response to peripheral vasodilation, because reflex beta-adrenergic stimulation overcomes the negative inotropic and chronotropic effects of the drug; this effect is commonly observed after verapamil administration in animals.[11,12] With larger doses of the drug, no change or small decreases in ventricular performance are observed, as reflex responses are offset by the depressant effects of verapamil[32]; this finding accounts for the effects of the drug in human beings. In patients not receiving other cardioactive drugs, verapamil decreases systemic vascular resistance without consistent improvements in cardiac output associated with decreases in mean systemic arterial pressure without increases in heart rate; furthermore, left ventricular dP/dt max may decrease and right and left ventricular filling pressures may increase, reflecting verapamil's negative inotropic effects.[30–36] With very large doses of the drug beyond the therapeutic range, contractile force and heart rate decrease markedly despite concomitant decreases in systemic vascular resistance, as sympathetic responses are overwhelmed by direct effects of the drug on the myocardium.[32,37,38] Clinicians have long feared that such deleterious circulatory responses might occur with smaller doses of verapamil (within the therapeutic range) if beta-adrenergic reflexes were pharmacologically attenuated.

Hemodynamic Studies of Combined Therapy

Effects of verapamil in patients receiving small doses of propranolol: To determine the hemodynamic effects of combined verapamil-propranolol therapy in patients receiving small doses of beta-adrenergic antagonists, Kieval et al.[39] evaluated 20 patients with chronic stable angina pectoris during diagnostic cardiac catheterization. All patients were treated with oral propranolol in doses ranging from 40 to 480 mg daily (mean 160 ± 92 mg). After right- and left-sided cardiac catheterization and contrast left ventricular angiography were performed and a stable control period was achieved, all patients received verapamil intravenously, initially as a bolus of 0.025 to 0.100 mg/kg and subsequently as a continuous infusion of 0.005 mg/kg/min of the drug for 45 minutes. Hemodynamic and cineangiographic variables were measured again at the end of the infusion period. The left ventricular ejection fraction ranged from 43 to 79%.

Verapamil produced significant decreases in mean arterial pressure and systemic vascular resistance without changes in heart rate, cardiac output, right and left ventricular diastolic pressure or left ventricular systolic and diastolic volume, and ejection fraction (Fig. 1). Heart rate remained unchanged despite the decline in systemic blood pressure; cardiac output and left ventricular ejection fraction did not increase despite a significant decrease in systemic vascular resistance. The mean plasma level of verapamil in this study was 161.8 ± 21.5 ng/ml and the mean plasma level of propranolol was 65.7 ± 13.9 ng/ml.

Six of the 20 study patients experienced notable decreases in systemic blood pressure (below 90 mm Hg systolic in 2 patients), but all of these episodes were asymptomatic. No patient experienced signs or symptoms of congestive heart failure or evidence of advanced atrioventricular block. Kieval et al.[39] concluded that the administration of verapamil to patients receiving small doses of propranolol produces no significant negative inotropic and chronotropic effects.

The effects of verapamil noted by Kieval and associates differ from those observed by Ferlinz et al.[30] in

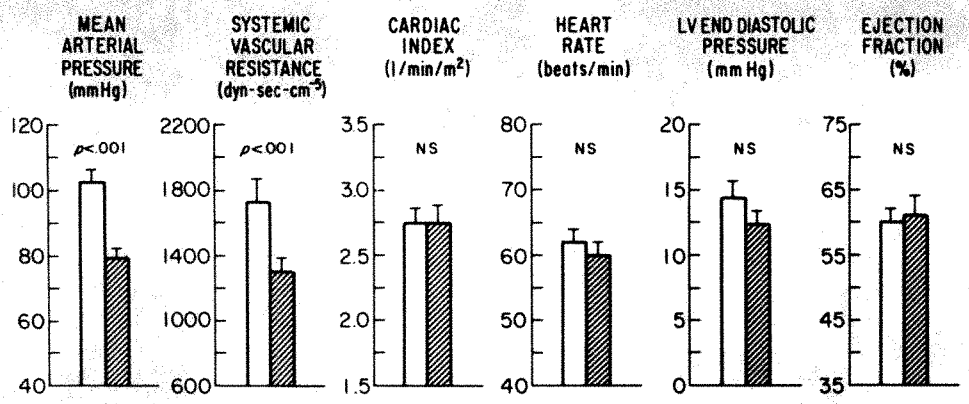

FIGURE 1. Values for mean arterial pressure, systemic vascular resistance, cardiac index, heart rate, left ventricular (LV) end-diastolic pressure, and ejection fraction before (**clear bars**) and after (**shaded bars**) the administration of verapamil intravenously to patients receiving small doses of propranolol (mean 160 mg daily). Significance of differences are shown by the p values **above the bars**. Group data are expressed as mean ± standard error of the mean (SEM). NS = not significant.

patients with coronary artery disease not receiving propranolol. Using a similar protocol in 20 patients undergoing diagnostic cardiac catheterization, Ferlinz and associates found that cardiac output and ejection fraction *increased* in association with drug-induced declines in peripheral resistance, and the decreases in mean arterial pressure were only half as great as those Kieval and associates had observed when the drug was administered with propranolol.[39] Accordingly, Kieval et al.[39] suspected that concomitant therapy with propranolol prevented the improvement in cardiac performance that was expected to accompany the peripheral vasodilator effects of verapamil.

It is unclear whether the lack of improvement in cardiac performance observed by Kieval et al.[39] was the result of concomitant propranolol therapy or the direct cardiodepressant effects of verapamil itself, largely because the findings of Ferlinz et al.[30] differ from those of other investigators who evaluated the effects of verapamil alone in patients with and without heart disease. Singh and Roche,[33] Atterhog and Ekelund,[34] Lewis et al.,[35] and Kellett et al.[36] noted little change in cardiac output, stroke volume, or ejection fraction after verapamil alone despite significant decreases in systemic vascular resistance; such findings are similar to those observed by Kieval et al.[39] in patients receiving concomitant therapy with propranolol. Furthermore, in these four studies, verapamil alone induced significant decreases in left ventricular dP/dt max and increases in right and left ventricular filling pressures.[33–36] The weight of the evidence, therefore, suggests that concomitant therapy with small doses of propranolol does not add significantly to the direct negative inotropic effects of intravenous verapamil alone in patients with preserved left ventricular function.

Effects of verapamil in patients receiving moderate doses of propranolol: To evaluate this interaction further, Leon et al.[40] investigated the effects of combined verapamil-propranolol therapy in patients receiving somewhat larger doses of propranolol. Eleven patients with stable angina of effort not satisfactorily controlled by propranolol alone were evaluated in a randomized triple cross-over study that compared the effects of placebo, propranolol, and verapamil followed by combined verapamil and propranolol. The doses of propranolol alone and in combination with verapamil were 160 to 320 mg daily (mean 255 mg); these doses had previously been individually titrated so as to produce optimal clinical responses without adverse effects, and all patients had resting heart rates less than 60 beats/min. The dose of verapamil used alone and in combination with propranolol was 480 mg daily orally except in 3 patients who received only 320 mg daily during combined therapy with propranolol.

As part of this clinical investigation, Bonow et al.[41] evaluated the effects of placebo, verapamil, propranolol, and combined therapy on left ventricular ejection fraction at rest and during exercise by radionuclide cineangiography before and 48 hours after therapy with each drug regimen. The left ventricular ejection fraction at rest during placebo period averaged 48.4 ± 2.8% (range 32 to 69%) and decreased to 43.4 ± 3.7% ($p < 0.01$) with combined verapamil-propranolol therapy, but these values were similar to those with verapamil alone (43.6 ± 3.6%) (Fig. 2). Five of the 11 patients had a decrease in ejection fraction greater than 5% with verapamil alone; none of them showed any additional decrease during concomitant treatment with propranolol. The ejection fraction during maximal exercise on combined therapy (41.2 ± 2.5%) was similar to that observed during placebo therapy (40.7 ± 3.4%), verapamil alone (41.9 ± 3.4%), or propranolol alone (40.6 ± 2.4%).

Systolic blood pressure at rest measured supine at the time of the radionuclide study decreased from 137.6 ± 7.1 to 117.5 ± 4.6 mm Hg with combined verapamil-propranolol therapy, but these values were similar to those with verapamil alone (120.7 ± 5.4 mm Hg) (Fig. 3). There were no significant decreases in ejection fraction or systolic blood pressure (compared with

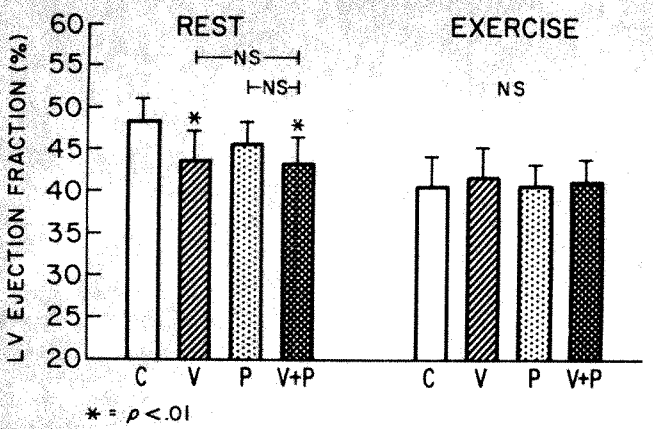

FIGURE 2. Values for left ventricular (LV) ejection fraction during rest and exercise after 48 hours of therapy with placebo (C), verapamil (V), moderately large doses of propranolol (P, mean 255 mg daily), and their combination (V + P) in 11 patients who completed a randomized triple cross-over study. **Asterisks** refer to significance of differences of treatment phases when compared with placebo periods. Values **above the bars** denote significance of differences *between* treatment periods, where NS = not significant. Group data are expressed as mean ± SEM.

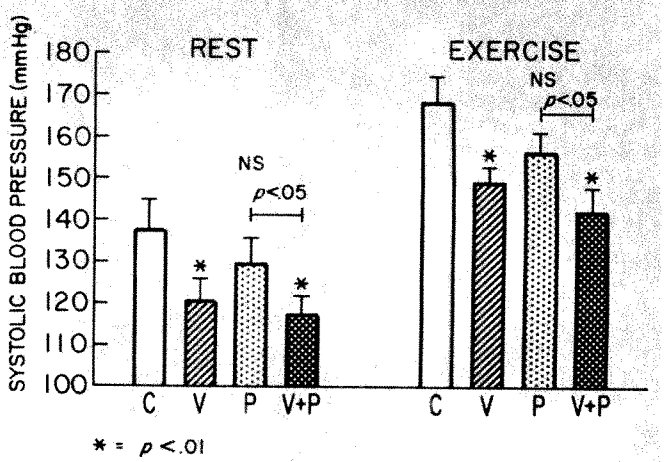

FIGURE 3. Values for systolic blood pressure during rest and exercise in the patients referred to in Figure 2. Format, symbols, and abbreviations as in Figure 2.

placebo) with propranolol alone. The heart rate at rest decreased from 78 to 57 beats/min ($p < 0.01$) with combined therapy, but this was similar to the heart rate during treatment with propranolol alone; verapamil alone produced only mild decreases in heart rate (78 to 71 beats/min, $p < 0.05$).

Of the 11 patients who received combined therapy, 3 had symptomatic adverse reactions. Two patients had orthostatic dizziness, which limited the maximal doses that could be administered. Two patients (1 of whom also had dizziness) had exertional dyspnea; 1 had the lowest pretreatment ejection fraction (32%) of any patient in the study, and 1 had the most marked decrease in ejection fraction (46 to 31%) with verapamil alone with subsequent heart failure during long-term treatment with the drug. Two patients, who experienced atrioventricular dissociation on verapamil alone, never received combined therapy.

The findings of Bonow et al.[41] that combined therapy with verapamil and propranolol produces decreases in ejection fraction and blood pressure similar to those observed with verapamil alone, support the concept that the failure to observe significant improvements in cardiac performance in response to the peripheral vasodilator effects of verapamil is primarily due to verapamil and is not the result of the additive negative inotropic effects of propranolol. This was the finding despite mean propranolol levels in this study (203 ± 33 ng/ml) which were 3 times higher than those observed by Kieval et al.[39]; however, the mean verapamil levels were similar (209 ± 29 ng/ml).

Effects of verapamil in patients receiving large doses of propranolol: To extend these observations to patients taking very large doses of propranolol, Packer et al.[42] evaluated the hemodynamic effects of combined therapy in 15 patients with severe angina at rest. All patients were being treated with large doses of propranolol (160 to 1,280 mg daily, mean 502 mg in 13 patients) or metroprolol (400 mg daily in 2 patients); only 3 of the 13 patients taking propranolol received doses less than 320 mg orally. After right heart catheterization was performed, a stable hemodynamic state was established, and small doses of verapamil were administered to ensure the safety of combined therapy, each patient received single doses of 120 mg of verapamil at 6 to 12 hour intervals; beta-adrenergic antagonists were administered together with the first 120 mg dose of verapamil and then were discontinued. Radionuclide angiographic determinations of left ventricular ejection fraction on propranolol before therapy with verapamil ranged from 35 to 78%.

The first 120 mg dose of verapamil, administered concomitantly with beta-blocking drugs, significantly decreased cardiac index (0.38 liters/min/m^2), stroke volume index (2.8 ml/beat/m^2), heart rate (6 beats/min), and mean arterial pressure (13.2 mm Hg) associated with increases in pulmonary capillary wedge pressure (2.2 mm Hg) and mean right atrial pressure (1.7 mm Hg), all significant at $p < 0.001$ (Fig. 4 and 5); there were no significant changes in systemic vascular resistance. Similar cardiodepressant effects were observed when 120 mg doses of verapamil were readministered 6 hours after beta-blockade withdrawal. The duration of these hemodynamic effects was brief; decreases in cardiac index and heart rate generally persisted only 2 to 3 hours, returning to control values within 4 hours after oral administration. The plasma levels of verapamil after the first administration of 120 mg of the drug were 205.1 ± 40 ng/ml, which were comparable to those noted by Kieval et al.[39] and Bonow et al.,[41] but plasma levels of propranolol were 474.1 ± 84 ng/ml, 2 to 7 times higher than those that characterized patients in these previous studies.

In contrast to the cardiodepressant effects observed when verapamil was administered with beta-blocking drugs, verapamil produced no significant decreases in

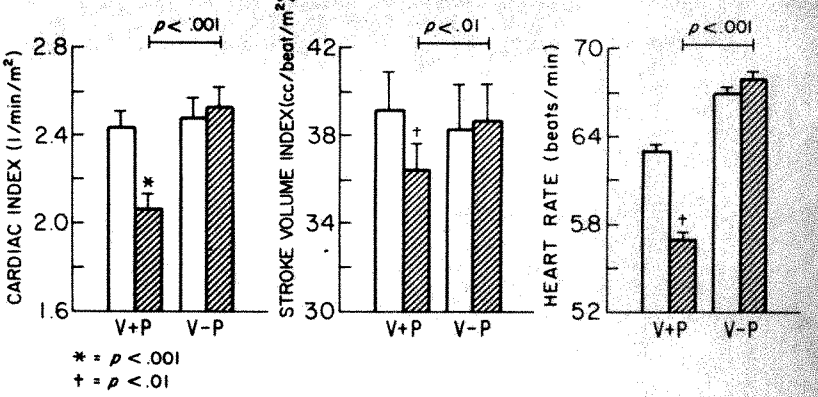

FIGURE 4. Effects of oral verapamil (120 mg) on cardiac index, stroke volume index, and heart rate in 15 patients during therapy with large doses of propranolol (mean dose of 502 mg daily) or metoprolol (400 mg daily), both denoted by V + P, and in the same patients again 30 hours after beta-blockade withdrawal, denoted by V−P. Control values before verapamil are shown in **clear bars** and the effects of verapamil are shown in **shaded bars.** **Symbols** denote significance of effects seen after verapamil compared with their respective controls. p values **above the bars** denote significance of differences between the effects of verapamil during treatment with and after withdrawal of beta-blocking drugs. Group data are expressed as mean ± SEM.

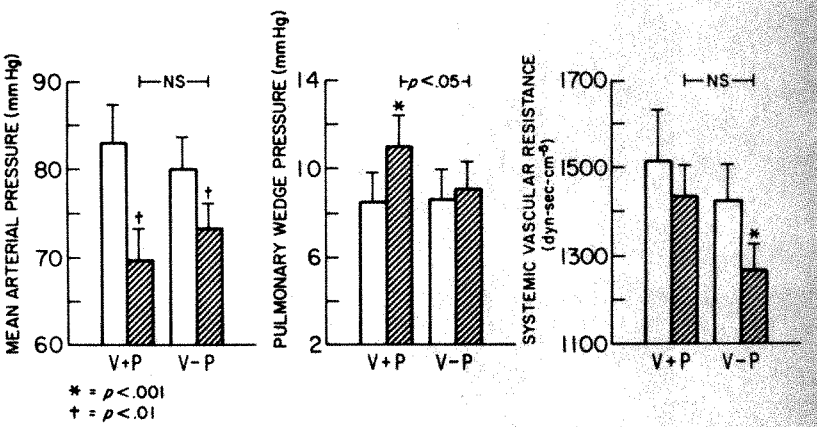

FIGURE 5. Effects of oral verapamil (120 mg) on mean arterial pressure, pulmonary capillary wedge pressure, and systemic vascular resistance in the 15 patients in Figure 4. Format, symbols, and abbreviations as in Figure 4.

cardiac index, stroke volume index, or heart rate and little change in pulmonary capillary wedge and mean right atrial pressures when administered 24 to 30 hours after withdrawal of beta blockade (Fig. 4 and 5). Mean arterial pressure decreased with verapamil not because of a decrease in cardiac output (as during combined therapy) but because of a decline in systemic vascular resistance. These circulatory responses were virtually identical to those noted by Kieval et al.[39] in their patients taking small doses of propranolol; this finding is consistent with the observation that plasma levels of propranolol 24 to 30 hours *after* beta blockade withdrawal in the study by Packer et al.[42] (41 ± 11 to 72 ± 20 ng/ml) were similar to levels seen *during* low dose propranolol therapy in the study by Kieval et al.[39] The progressive decline in the cardiodepressant effects of verapamil (as plasma propranolol levels decreased) was especially remarkable, because plasma *verapamil* levels concomitantly *increased* (from 205 ± 40 to 383 ± 51 ng/ml) with repeated doses of the drug as beta-blocking agents were withdrawn; such higher levels of verapamil would have by themselves been expected to produce *greater* cardiodepressant effects.

Adverse clinical reactions, all of them asymptomatic, were observed in 3 of the 15 patients: 1 patient had transient junctional bradycardia with combined therapy but not with verapamil alone (no additive effects on atrioventricular conduction were noted in the other 14 patients); 2 patients had marked but asymptomatic decreases in mean blood pressure (of 30 and 59 mm Hg) after the first 120 mg dose of the drug, and both had received methyldopa within the past 7 days. In none of the 15 patients did signs or symptoms of congestive heart failure develop during combined drug treatment.

The history of recent methyldopa therapy in the two patients who had hypotensive reactions is of interest. In the intact circulation, verapamil's peripheral vasodilator effects serve to offset its cardiodepressant actions by reflex beta-sympathetic stimulation; thus, only mild hypotension is usually seen with verapamil alone (Fig. 6, top). If beta-adrenergic reflexes are blocked by concomitant propranolol therapy, however, these negative inotropic and chronotropic actions remain unopposed and could combine with the peripheral vasodilator effects of the drug to produce profound hypotension. However, it is likely that the circulation acts to prevent this reaction during combined therapy by reflex *alpha*-sympathetic stimulation which, by producing peripheral arterial and venous vasoconstriction, offsets the direct peripheral vascular effects of the drug (Fig. 6, bottom). This fact explains why verapamil failed to reduce systemic vascular resistance in patients receiving large doses of beta-sympathetic antagonists, but did so after their withdrawal; similar findings were noted in animal models by Rowe et al.[13] This peripheral vaso-

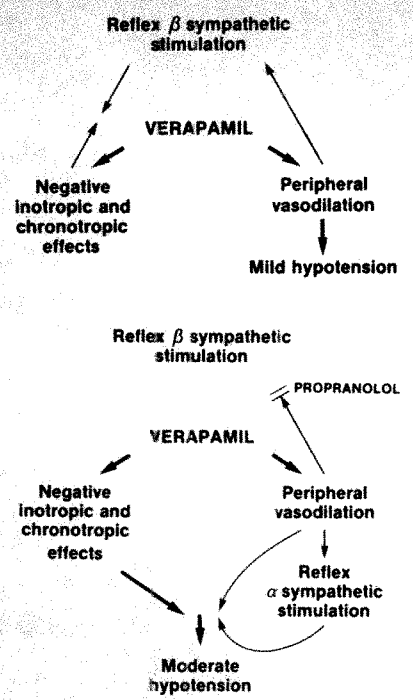

FIGURE 6. Top, diagram showing the effects of verapamil in the absence of beta-blockade. Reflex beta-sympathetic stimulation serves to offset the direct negative inotropic and chronotropic effects of the drug. **Bottom,** diagram showing the effects of verapamil during the administration of beta-adrenergic antagonists. Propranolol blocks beta-sympathetic reflexes and thus leaves the direct cardiodepressant effects of verapamil unopposed. These can summate with the drug's peripheral vasodilator effects and produce profound hypotension unless verapamil's peripheral actions were in turn opposed by activation of alpha-adrenergic reflexes.

constriction probably contributes to the increases in right and left ventricular filling pressures seen with combined therapy but not with verapamil alone. Such observations may account for the marked decreases in blood pressure that may be noted during combined treatment when alpha-sympathetic responses are attenuated as would occur after recent methyldopa or quinidine therapy.[26,43]

Conclusions of hemodynamic studies: The combined experience from the three foregoing clinical studies leads us to the following conclusions. In patients with preserved left ventricular function, verapamil produces little change in cardiac performance in most patients with coronary artery disease not receiving beta-receptor antagonists; however, significant decreases in ejection fraction (more than 5%) may occasionally be seen and may result in clinical congestive heart failure. Verapamil produces little change or mild decreases in cardiac performance in patients receiving small doses of propranolol; these hemodynamic effects probably do not differ from those that would be observed in these patients with verapamil alone. Verapamil produces modest but significant cardiodepressant effects in patients taking large doses of propranolol; such deleterious effects can be avoided by withdrawal of propranolol for 24 hours.

Our observations indicate that the magnitude of the adverse interaction between verapamil and propranolol depends greatly on the dose of propranolol administered. This fact suggests that large doses of propranolol are needed to attenuate beta-adrenergic reflexes sufficiently to leave verapamil's negative inotropic effects unopposed. Such a concept conflicts with the work of Chidsey et al.[44] who reported that near maximal beta-blockade is achieved with relatively small doses of propranolol (such as 160 mg daily) and low plasma levels of the drug (75 to 100 ng/ml). However, if this were the case, we would have expected similar cardiodepressant effects of combined therapy in all of our studies; our findings that adverse interactive hemodynamic effects were dose-related could then only be explained by assuming that propranolol exerts negative inotropic effects independent of its effects on beta-adrenergic receptors, which it does not do in clinically relevant doses.[45,46] Rather, our findings are more consistent with the work of Goldstein et al.,[46] Shand,[47] and Coltart and Shand[48] who reported that the degree of beta-adrenergic blockade varies linearly with plasma propranolol concentrations, even up to levels exceeding 500 ng/ml.

Of the 46 patients who received short-term combined therapy in these three studies, there were 13 reactions in 12 patients that were of concern to the investigators. In 10 of these patients, *hypotension* was the adverse effect observed; congestive heart failure was observed in 2 patients and a cardiac conduction abnormality in one. Only 4 episodes in 3 patients (7%) were symptomatic and required a reduction in the dosage of verapamil; none of these was severe enough to require discontinuation of therapy.

The 7% frequency of symptomatic adverse reactions observed in these hemodynamic studies, however, may have underestimated the true frequency of such events. The duration of combined therapy in these studies was brief, and adverse clinical responses may be more frequent during more prolonged treatment. Furthermore, ventricular function in these patients before therapy was generally well preserved (all had an ejection fraction of 30% or greater); Chew et al.[49] have shown that the negative inotropic effects of verapamil may be most evident and precipitation of heart failure most likely in patients whose ejection fractions are less than 30%. The true incidence of adverse reactions with combined therapy can only be determined by careful observation and analysis of a far larger number of patients over longer periods of time.

Clinical Studies of Combined Therapy

Physiologic considerations: There is strong theoretic and clinical support for the use of combined verapamil and propranolol therapy in patients with angina pectoris. Propranolol exerts its effects primarily by its negative chronotropic and inotropic actions.[50] The drug markedly attenuates exercise-induced increments in double-product (primarily by decreasing heart rate) at submaximal and at maximal workloads.[50,51] However,

verapamil exerts its effects by decreasing ventricular afterload consequent to peripheral vasodilation,[52] by antagonizing coronary vasospasm,[3] and by improving diastolic function[41] rather than by primarily decreasing heart rate or contractility. Exercise-induced increments in double-product are attenuated by verapamil at submaximal workloads (primarily by decreasing blood pressure), but increments in double-product at maximal exercise are similar to those achieved before therapy, although at a substantially greater work load.[4,51,53] A combination of the two drugs, acting by different mechanisms, might then be expected to possess additive or synergistic effects on anginal symptoms.

We have already emphasized that the administration of verapamil to patients not receiving propranolol stimulates the beta-adrenergic nervous system, which serves to support circulatory homeostasis by opposing the direct cardiodepressant effects of verapamil. However, this increase in beta-sympathetic activity may detract from verapamil's antianginal actions by increasing heart rate and contractile force.[28] On the other hand, the administration of propranolol to patients not receiving verapamil inhibits beta-adrenergically mediated coronary vasodilation and consequently may exacerbate symptoms in patients in whom vasospasm is playing an important role.[54–56] Combined drug therapy may therefore produce synergistic benefits on anginal symptoms not only because each drug exerts independent antianginal effects but also because each may serve to oppose the concomitant unfavorable cardiovascular actions of the other.

Comparative clinical trials: Two randomized binded clinical trials compared the *effectiveness* of combined therapy with the benefits achieved by treatment with either drug used alone. In the study by Leon et al.,[40] the effects of placebo, propranolol, and verapamil on exercise duration and clinical symptoms were assessed using a randomized triple cross-over design in 11 patients with stable effort angina who remained symptomatic on propranolol alone; all patients had preserved left ventricular function (ejection fraction greater than 30%). The doses of propranolol ranged from 160 to 320 mg daily and had previously been individually titrated so as to produce resting heart rates less than 60 beats/min; the doses of verapamil were 320 to 480 mg daily. Exercise tolerance (evaluated by bicycle ergometry) was assessed under double-blind conditions after each drug had been administered for 48 hours. After the randomized phase of the trial was completed, patients were treated in an open-label fashion with their usual doses of propranolol to which verapamil (320 to 480 mg daily) was added, after which exercise capacity was reevaluated.

The mean duration of exercise was 5.1 ± 0.7 minutes with placebo, 6.5 ± 0.5 minutes with propranolol, and 8.5 ± 0.7 minutes with verapamil (480 mg daily); the differences among all 3 treatment groups were significant (Fig. 7). Patients exercised significantly longer on propranolol ($p < 0.05$) and verapamil ($p < 0.01$) than on placebo; exercise was stopped because of angina in 11

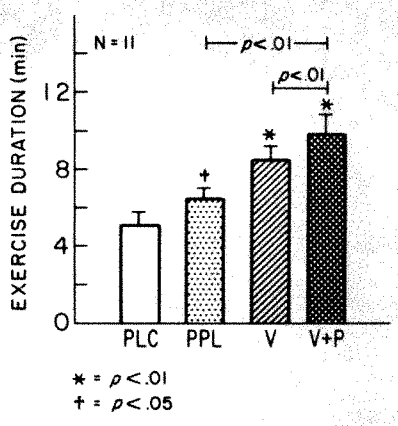

FIGURE 7. Exercise duration in 11 patients with angina of effort after 48 hours of therapy with placebo (PLC), propranolol (PPL), verapamil (V), and combined verapamil and propranolol treatment (V + P) evaluated by a randomized triple cross-over design. **Symbols above the bars** denote significance compared with placebo therapy; **p values above the bars** denote significance between the treatment groups. Group data are expressed as mean ± SEM.

patients on placebo, 9 on propranolol, and 10 on verapamil. When verapamil (mean dose 407 mg daily) was added to propranolol, exercise duration increased to 9.8 ± 1.0 minutes. This duration was significantly better than that with either propranolol alone ($p < 0.01$) or verapamil alone ($p < 0.01$); only 2 of the 11 patients with combined therapy had angina during exercise. The investigators concluded that the addition of verapamil to patients receiving propranolol improved exercise tolerance over that observed with either agent used alone.

Bala Subramanian et al.[57] evaluated the effects of individual and combined verapamil-propranolol therapy in 14 patients with stable effort-related angina pectoris, all of whom had preserved left ventricular function (ejection fraction greater than 30%). Initially, 22 patients entered a 2 week single-blind placebo run-in period; an 8 week double-blind trial followed, consisting of 4 weeks of treatment with either verapamil or propranolol, followed by cross over to the alternate drug for an additional 4 weeks. Fourteen of the 22 patients who still had exertional angina during both of the individual treatment periods then received 4 weeks of treatment with both verapamil and propranolol administered in a single-blind fashion. The dose of propranolol was 120 mg daily and that of verapamil 360 mg daily. Exercise capacity was assessed by the duration of exertion on a treadmill at the end of each of the three 4 week treatment periods. One of the 14 patients failed to complete the trial of combined therapy because congestive heart failure developed.

The mean exercise time for these patients while taking placebo was 4.8 ± 0.2 minutes and increased to 6.8 ± 0.6 minutes with propranolol ($p < 0.01$), to 8.0 ± 0.5 minutes with verapamil ($p < 0.01$), and to 10.1 ± 0.9 minutes with combined verapamil-propranolol therapy ($p < 0.01$); the improvement in exercise tolerance with

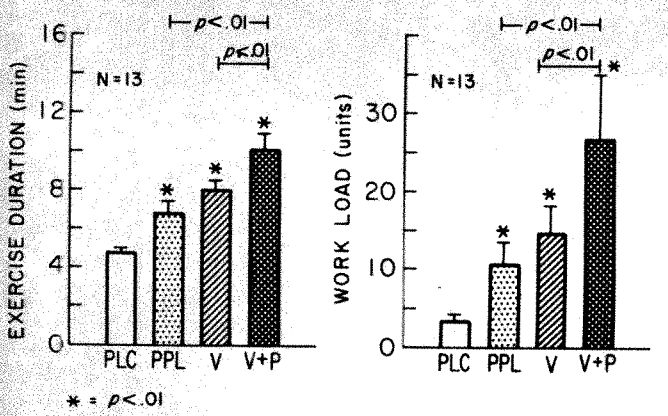

FIGURE 8. Exercise duration and work load achieved in 13 patients with angina of effort after 4 weeks of therapy with placebo (PLC), propranolol (PPL), verapamil (V), and combined verapamil and propranolol treatment (V + P) evaluated by a double-blind randomized cross-over protocol. **Symbols above the bars** denote significance compared with placebo therapy; **p values above the bars** denote significance between the treatment groups. Group data are expressed as mean ± SEM.

combined therapy was superior to that achieved with propranolol or verapamil alone, both $p < 0.01$ (Fig. 8). Because the exercise load was incremental and not linear, work load was calculated by multiplying distance walked in kilometers by the sine angle of treadmill in degrees and expressed in units. The work load achieved with combined therapy (26.7 ± 5.3 units) was substantially greater than that achieved with verapamil alone (14.7 ± 2.1), propranolol alone (10.7 ± 2.6), or placebo (3.5 ± 0.6). Seven of the 13 patients became angina-free with combined therapy. The investigators concluded that combined therapy was superior to either agent alone in patients who remained symptomatic on single-drug therapy.

The findings of both trials must be interpreted in the context of certain precautions and limitations. Patients were generally selected for combined verapamil-propranolol therapy after they remained symptomatic on treatment with either or both drugs alone. Hence, it is unclear whether exercise capacity is enhanced by combined therapy in patients who respond adequately to treatment with a single agent. Furthermore, the trials were conducted such that treatment with verapamil or propranolol alone was double-blinded, but combined therapy was administered under open-label or single-blind conditions; hence, the results might have been affected by both patient and observer bias. Finally, treatment with both drugs always followed therapy with each drug individually, primarily because of fears that combined therapy would produce adverse effects unless it could be shown that each patient tolerated single-agent therapy well. Hence, the greater benefits seen during combined treatment may have been the result in part of a training effect. Leon et al.,[40] however, excluded a training effect in their study.

Most importantly, the beneficial effects of combined verapamil-propranolol therapy in these two studies were observed in patients with preserved left ventricular function (ejection fraction greater than 30%). Bala Subramanian et al.[57] subsequently treated an additional 40 patients with severe exertional angina pectoris with combined therapy, who had severe left ventricular dysfunction (ejection fraction less than 30%). The doses used were verapamil 360 mg daily and propranolol 60 to 120 mg daily. Although many of these patients experienced clinical benefits not seen with either drug alone, adverse effects were observed in 10 of 40 patients (25%). These effects consisted of hypotension in 4 patients, cardiac failure in 3, bradycardia in 1, and a junctional rhythm in 2. These adverse effects were controlled by either discontinuation or reduction in the dose of propranolol. The high incidence of adverse reactions with combined therapy was directly attributable to the more compromised left ventricular function in these 40 patients.

Combined Therapy of Propranolol With Other Calcium Antagonists

The findings of the studies reported in this review apply only to combined therapy with verapamil and not necessarily to other slow calcium channel antagonists such as nifedipine and dilitiazem. Although nifedipine resembles verapamil in depressing slow channel activity in cardiac muscle,[58] it has minimal direct depressant effects on atrioventricular conduction,[32,58–60] and neutralization of its cardiac depressant effects by peripheral vasodilation seems to be more nearly complete with nifedipine than with verapamil[28]; hence, combined therapy with beta-adrenergic antagonists might be safer with nifedipine than with verapamil.

Available data, however, suggest that an adverse interaction also occurs between nifedipine and propranolol in a manner similar to that observed with verapamil and propranolol. Whereas nifedipine alone produces significant increases in ejection fraction, mean circumferential fiber shortening, and peak dP/dt in patients with ischemic heart disease,[61,62] *decreases* in peak dP/dt without change in ejection fraction or mean circumferential fiber shortening are seen after the administration of nifedipine to patients receiving beta-blocking drugs, even those with preserved left ventricular function.[63] Hence, reflex beta-adrenergic stimulation counteracts the intrinsic cardiodepressant effects of nifedipine as it does with verapamil.[28,63,64]

Elucidation of the nature of the hemodynamic interaction between nifedipine and beta-adrenergic antagonists is especially important in view of the increasing number of reports of adverse hemodynamic effects (hypotension and severe congestive heart failure) during nifedipine therapy in patients receiving beta-blocking agents[65–68]; in two reports, symptoms and signs of heart failure disappeared when nifedipine was withdrawn and reappeared when nifedipine was readministered.[65,68] Therefore, caution should be exercised whenever combined therapy of beta-blocking drugs and all calcium antagonists is contemplated.

Although combined nifedipine and propranolol therapy should provide benefits superior to those ob-

served with either drug alone, this result has not yet been confirmed. In the only controlled study that examines this question, Lynch et al.[69] showed that the combination of nifedipine and propranolol was superior to placebo in reducing episodes of angina in a 2 to 4 week double-blind trial; however, combination therapy was not clearly better than propranolol alone. Unfortunately, most patients in the study, as in the verapamil studies, were selected because they remained symptomatic with beta-blocking drug therapy alone. Moreover, the objective criteria of this study consisted only of the magnitude of S-T depression by precordial exercise mapping at a fixed work load and by ambulatory electrocardiographic monitoring; exercise tolerance was not evaluated. Hence, the advantages of combined nifedipine-propranolol therapy in effort-related angina remain unproved.

Hemodynamic and clinical studies of combined therapy of diltiazem and beta-adrenergic antagonists have not yet been reported, so that the safety and effectiveness of this approach is unknown.

Conclusions

Evidence presented in this review indicates that combined verapamil and propranolol therapy is effective in highly selected patients with coronary heart disease. In patients who remain symptomatic despite optimal therapy with propranolol and nitrates, we recommend substitution of verapamil for propranolol, because several well-controlled randomized double-blind trials show that verapamil is superior to propranolol with treatment of angina of effort and at rest.[51,57,70] Available data suggest that such substitution can generally be accomplished safely without the need to withdraw propranolol before instituting verapamil therapy. For patients taking large doses of propranolol, however, the administration of verapamil within 24 hours of the last dose of propranolol can produce significant cardiodepressant effects; therefore, such patients require careful observation of vital signs and cardiac rhythm during the first 24 hours of verapamil therapy, particularly if they have recently been treated with drugs (such as methyldopa or quinidine) that attenuate alpha-adrenergic responses.

In patients who remain significantly symptomatic despite adequate doses of verapamil alone, the addition of propranolol is likely to provide additional therapeutic benefits. Such therapy should be undertaken only in patients with preserved left ventricular function (ejection fraction greater than 30%); propranolol should be initiated in small doses and titrated upwards after careful reevaluation of vital signs and clinical status. In contrast to the present practice of using combined nitrate and beta-blocking drug therapy without the need to prove the effectiveness of either component alone, the experience with combined therapy of calcium antagonists and beta-blocking agents is as yet too limited to recommend its routine clinical use in patients who are responsive to either drug alone.

Until more evidence is available, combined therapy should be avoided or used with great caution after other therapeutic modalities have failed in the following: (1) patients with severe left ventricular dysfunction (ejection fraction of less than 30%); (2) patients with underlying atrioventricular conduction system disease; and (3) patients taking drugs that possess independent negative inotropic effects, such as disopyramide.

Thus, combined calcium channel and beta-adrenergic blockade provides important therapeutic benefits for many patients with severe angina pectoris. Adverse cardiovascular reactions during combined therapy may occur, however, so that more studies are needed to determine the frequency of such reactions and to identify those patients particularly susceptible to an unfavorable response. Until these studies are performed, patients being considered for combined therapy need to be carefully selected and observed.

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Hypertension and Hemodynamics: Therapeutic Implications.

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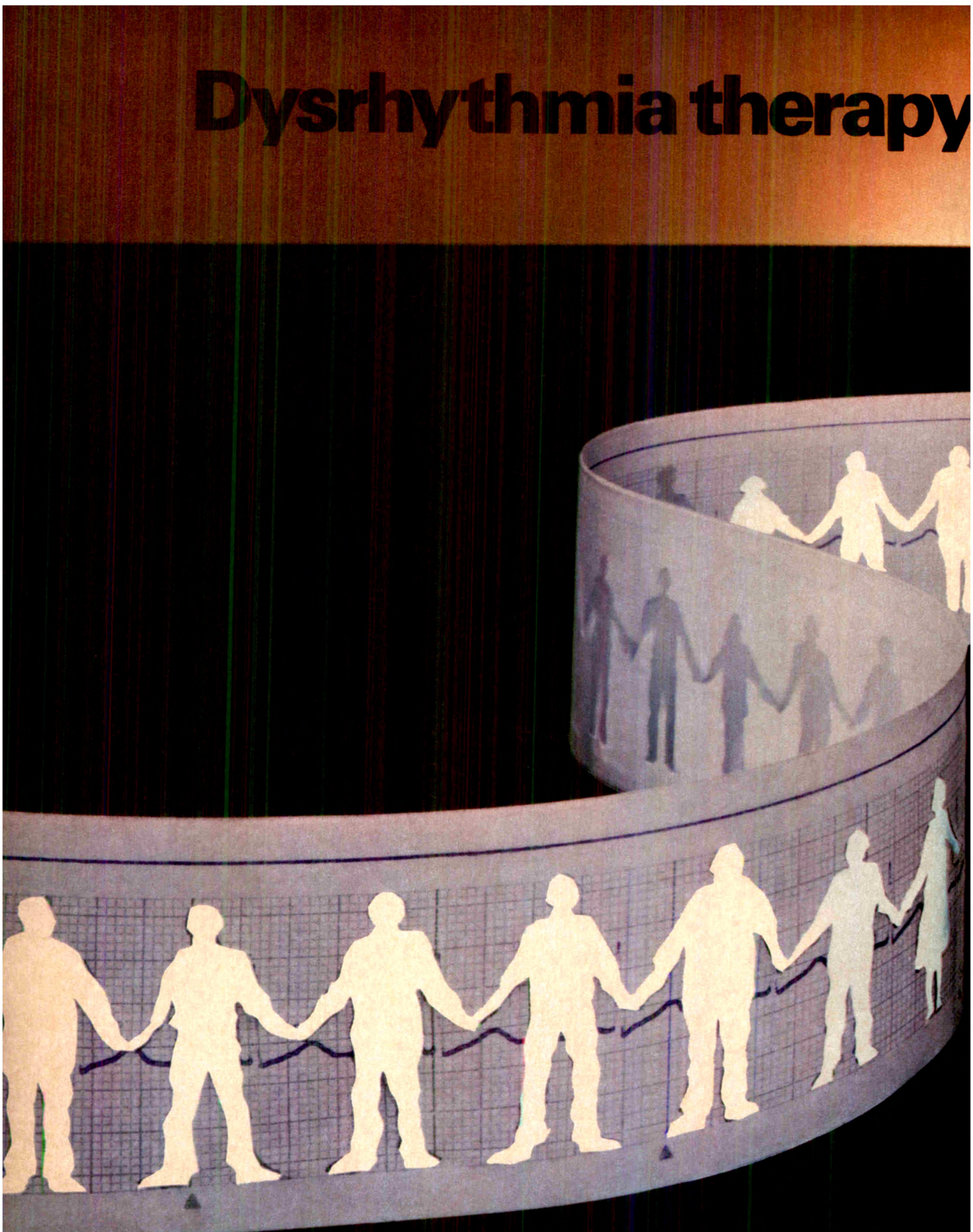

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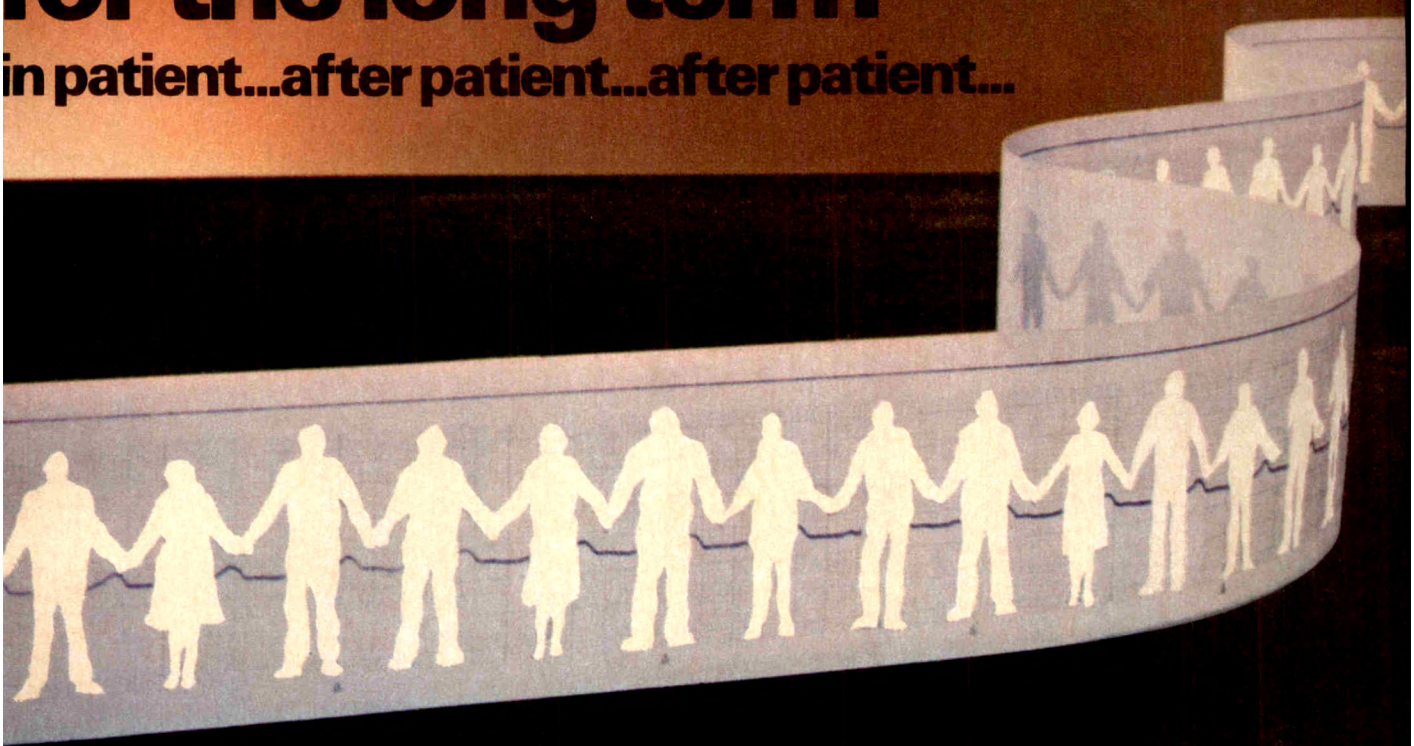

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Oral Norpace has not been adequately studied in patients with acute myocardial infarction or with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established. **Contraindications:** Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug. **Warnings: Norpace may cause or worsen congestive heart failure (CHF) or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily with primary cardiomyopathy or inadequately compensated CHF. Norpace should not be used in patients with uncompensated or marginally compensated CHF or hypotension unless the condition is secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace, but careful attention must be given to maintaining cardiac function, including optimal digitalization. If hypotension occurs or CHF worsens, Norpace should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace should be discontinued if significant widening (greater than 25%) of the QRS complex occurs. Prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. If Q-T prolongation greater than 25% is observed and if ectopy continues, the patient should be monitored closely, and discontinuation of Norpace considered. In rare instances significant hypoglycemia has been reported during Norpace therapy. The concomitant use of Norpace with other Type 1 antiarrhythmic agents should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. Patients receiving more than one antiarrhythmic drug must be carefully monitored. If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of benefit versus risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic activity, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.** **Precautions:** Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage. Antiarrhythmic drugs may be ineffective in patients with hypokalemia, and their toxic effects may be enhanced in patients with hyperkalemia. Therefore, potassium abnormalities should be corrected before starting Norpace therapy. Safe use in pregnancy has not been established. Disopyramide has been found in human fetal blood. **Norpace has been reported to stimulate contractions of the pregnant uterus.** Use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. Following oral administration, disopyramide has been found in human milk at a concentration not exceeding that in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted. Effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown. Safety and effectiveness of Norpace in children have not been established. **Adverse Reactions:** Dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention, urinary frequency and urgency, impotence, nausea, pain/bloating/gas, anorexia, diarrhea, vomiting, nervousness, dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains, hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain, generalized rash/dermatoses, itching, hypokalemia, elevated cholesterol/ triglycerides, depression, insomnia, dysuria, numbness/tingling, elevated liver enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, and hypoglycemia. Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported. **Dosage and Administration:** Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours. If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually with close monitoring. **See current complete prescribing information for dosage recommendations, including pediatric use. How Supplied:** Capsules containing 100 mg or 150 mg of disopyramide base.

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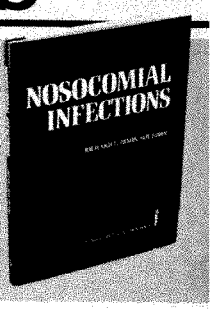

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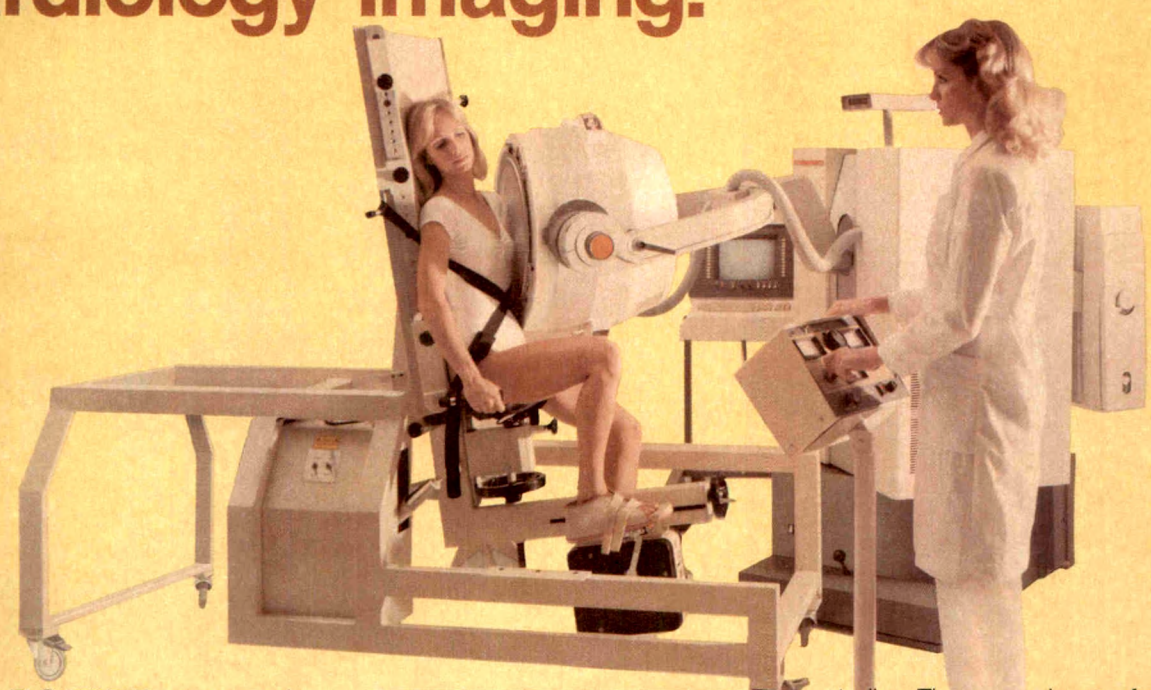

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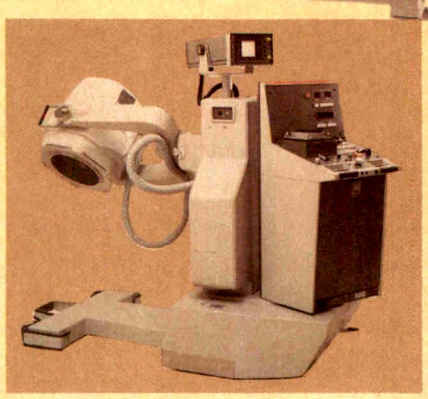

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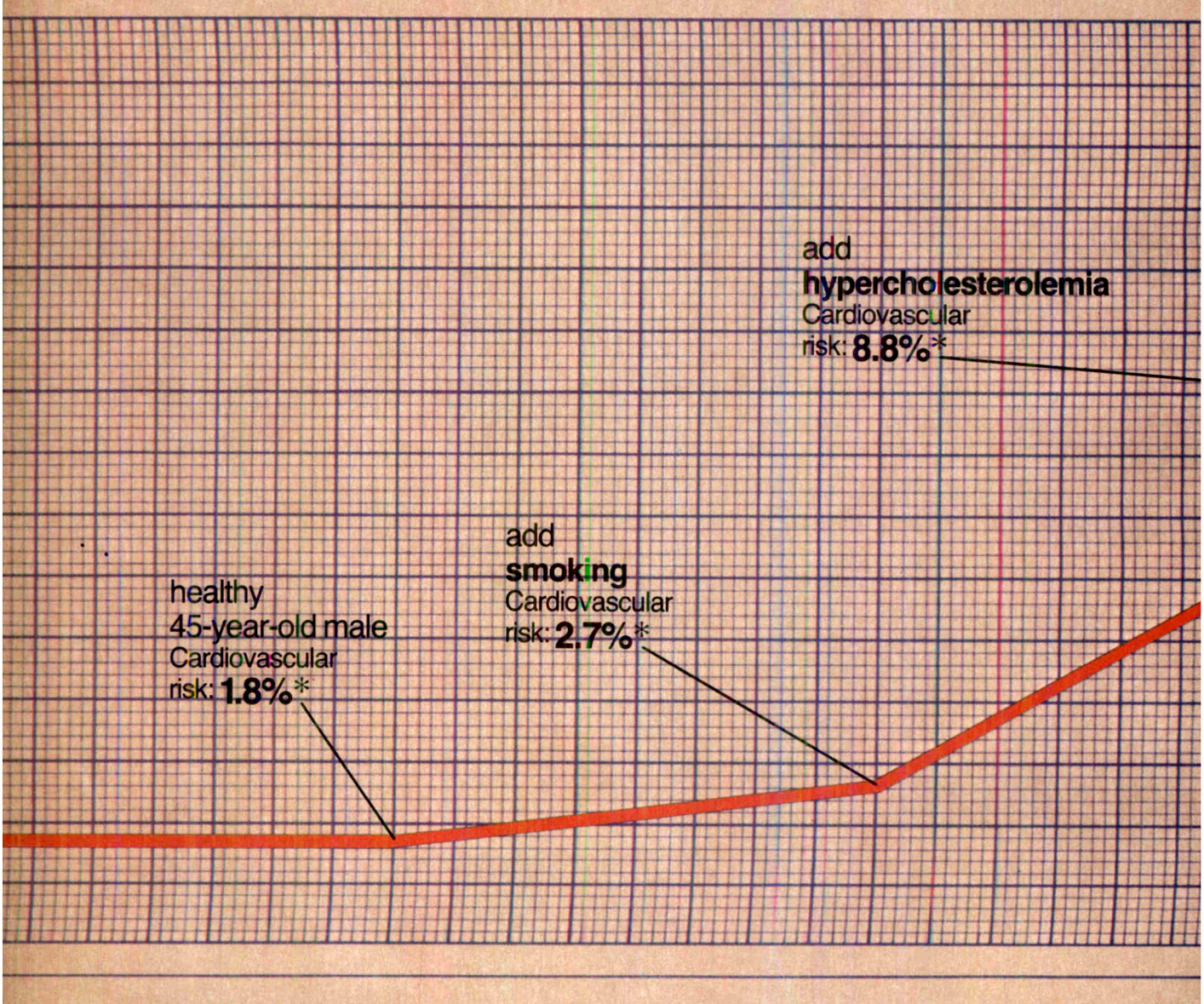

Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

*Percent equals chances in 100 of developing coronary heart disease within 6 years.

Adapted from *Coronary Risk Handbook:* Estimating risk of coronary heart disease in daily practice. 1973, American Heart Assoc., Inc.

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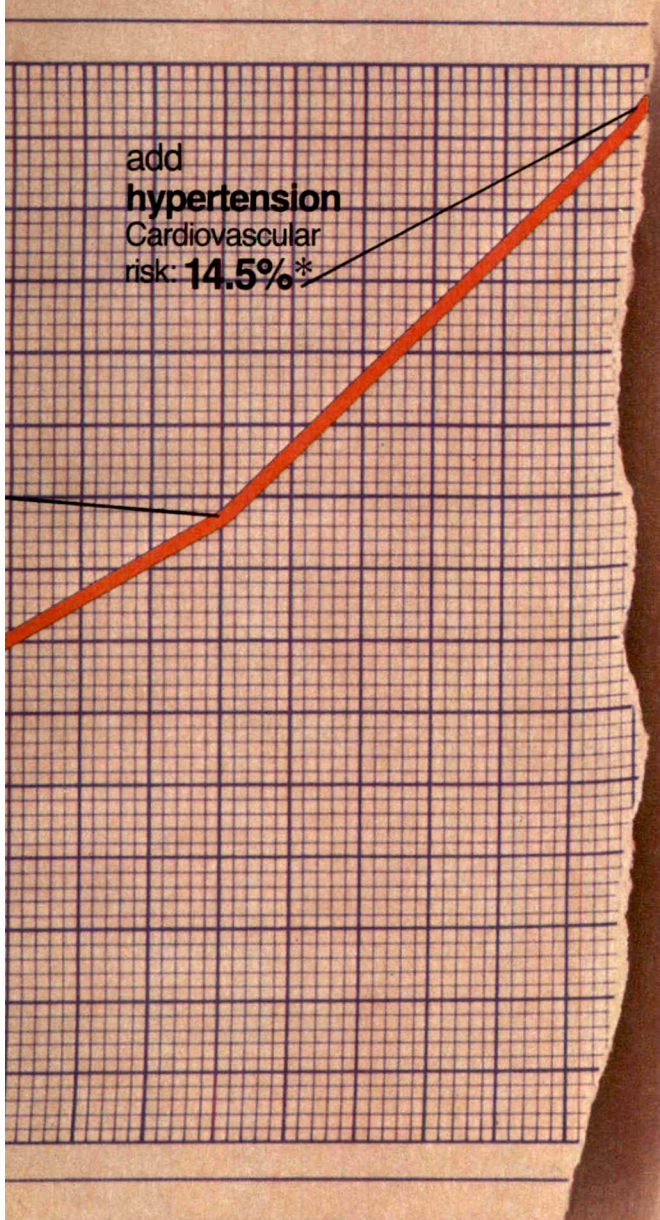

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BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*
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WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established.)

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus, alopecia, lichen planus.

Genitourinary: urinary frequency, incontinence, impotence, priapism.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings.)

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

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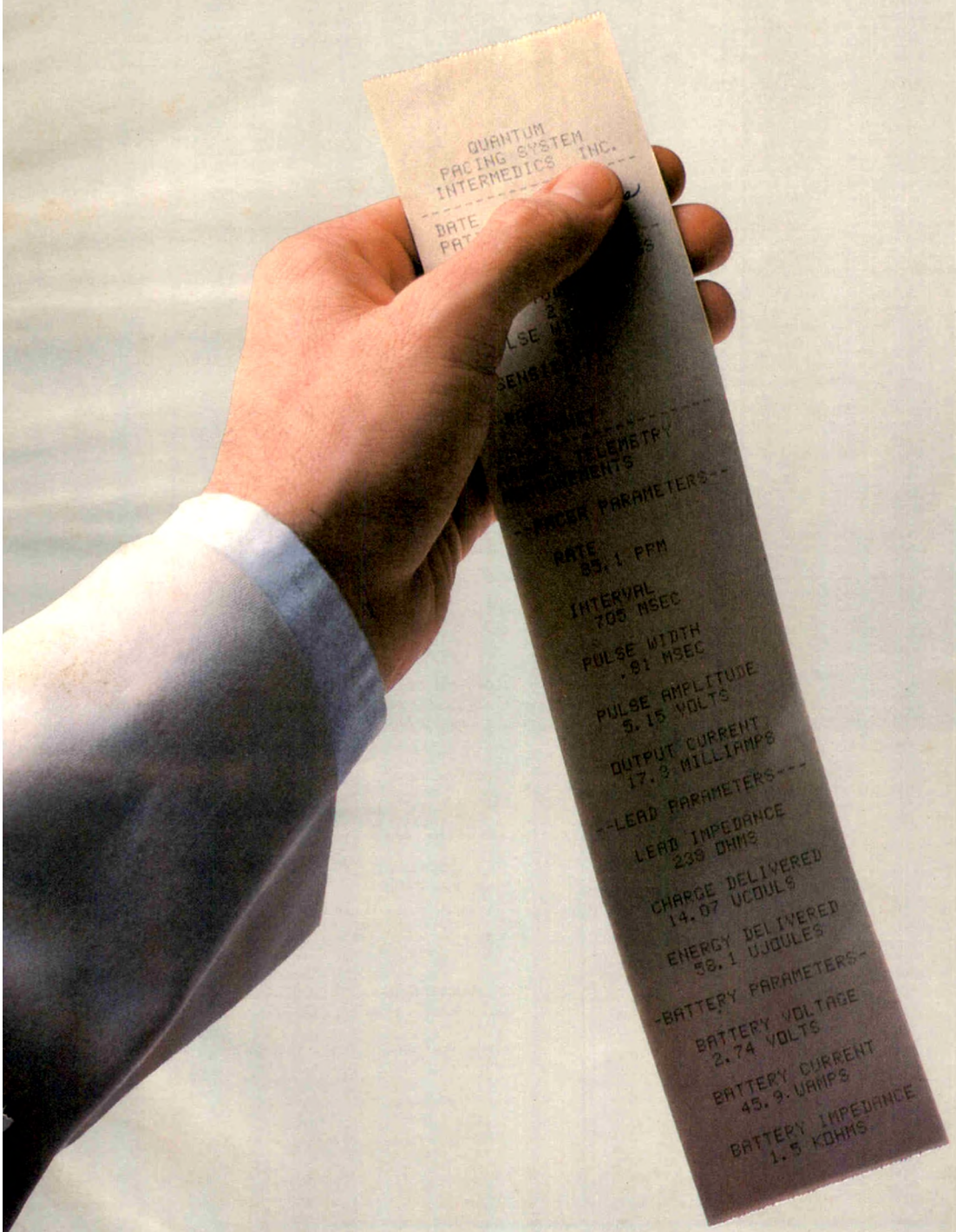

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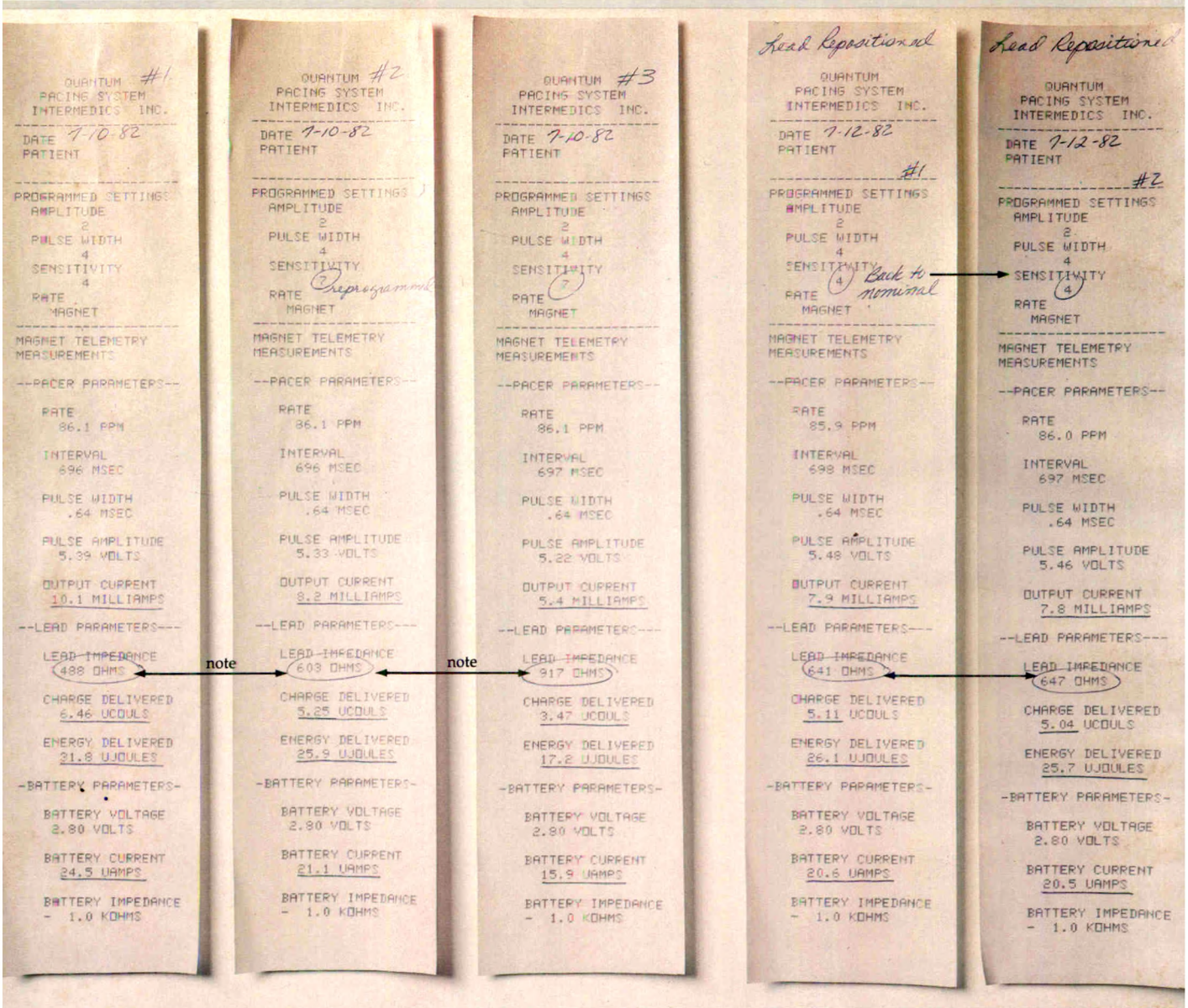
Quantum™ Telemetry Uncovers Lead Instability



An Actual Case History*

Patient: MALE
Age: 81 YEARS
Diagnosis: HEART BLOCK, BRADYCARDIA WITH EPISODES OF VENTRICULAR TACHYCARDIA
Indication for Pacing: ARRHYTHMIA (BRADYCARDIA) CONTROL

The patient received a Quantum model 253-09 pulse generator with a transvenous unipolar lead. Intra-operative fluoroscopy and threshold testing indicated acceptable lead position.

Eighteen hours post implant, telemetry measurements displayed lead parameters that fluctuated widely, as shown in three successive telemetry printouts. The patient was uncomfortable and while there was no evidence of loss of capture on the EKG, pacing and sensing were irregular. Further investigation and discussion between the cardiologist and implanting surgeon led to a decision to reposition the lead. Repositioning surgery was successful.

Normal pacing and sensing were observed after repositioning. Successive telemetry measurements showed stable lead parameters, verifying that a more satisfactory position had been achieved. The patient was discharged following good post-operative recovery and subsequent telemetry follow-up demonstrated chronic lead stability.

*This actual case history is on record at Intermedics, Inc. For more information, contact the Marketing Dept., Intermedics, Inc.

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Verapamil Therapy for Prinzmetal's Variant Angina: Comparison With Placebo and Nifedipine

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This study was performed (1) to assess the efficacy and safety of verapamil in patients with variant angina, and (2) to compare verapamil and nifedipine in patients with this clinical syndrome. In 27 patients, placebo and verapamil were administered in a long-term, randomized, and double-blind study of 9 months' duration. In comparison to placebo, verapamil reduced the frequency of angina, nitroglycerin usage, transient episodes of electrocardiographic S-T segment deviation (as assessed by 2-channel Holter monitoring), and hospitalizations required for clinical instability. Subsequently, 23 patients were treated with nifedipine in a nonblind fashion for 2 months, and this agent exerted a beneficial effect similar to that of verapamil. Finally, gated equilibrium blood pool scintigraphy, performed in 10 patients at rest and during exercise during treatment with placebo, verapamil, and nifedipine, demonstrated that neither calcium antagonist caused a deterioration of left ventricular performance. Thus, (1) long-term oral verapamil and nifedipine are each superior to placebo and are of similar efficacy in patients with variant angina, and (2) neither agent adversely influences left ventricular performance in patients with relatively normal left ventricular function.

Over the past 15 to 20 years, a group of pharmacologic agents known as calcium channel antagonists have been used outside the USA for the treatment of several forms of coronary heart disease.[1,2] These agents inhibit the movement of calcium from the extracellular to the intracellular space in cardiac and arterial smooth muscle and, as a result, may diminish both arterial tone and myocardial contractility. Of the available calcium blocking drugs, verapamil and nifedipine appear promising in the therapy of ischemic heart disease. Although preliminary experience shows that these drugs are especially effective in patients with variant angina,[3–9] these clinical trials have been uncontrolled or have administered the drugs for short periods of time; furthermore, no attempt has been made to compare verapamil and nifedipine in patients with this clinical syndrome.

Both verapamil and nifedipine possess direct negative inotropic effects in isolated cardiac muscle preparations[10,11]; however, neither agent exerts important negative inotropic effects in vivo, largely because of the direct systemic vasodilator actions exerted by both drugs,[11,12] which, by stimulating sympathetic reflexes and reducing ventricular afterload, offset the negative effects of these agents on myocardial contractility.[13–16] Although differences between the effects of verapamil and nifedipine on cardiac performance are thought to exist,[17] these beliefs are based largely on acute studies using large doses of both drugs administered parenterally; the *long-term* effects of *oral* administration of these drugs on ventricular function have not been compared in the same patients with angina pectoris.

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The present study was designed to address three questions: (1) Is verapamil a safe and effective pharmacologic agent in patients with variant angina? (2) Are verapamil and nifedipine of similar efficacy in patients with this clinical syndrome? and (3) Does the long-term oral administration of verapamil or nifedipine exert a depressant effect on left ventricular performance in patients with variant angina?

Methods

Long-term, randomized, and double-blind comparison of placebo and verapamil in patients with variant angina: Twenty-seven patients (19 men, 8 women, average age 52 years) with recurrent episodes of angina at rest and concomitant transient S-T segment elevation were enrolled in a comparison of placebo and verapamil (450 ± 16 mg/day in 3 to 4 divided doses, mean ± standard error of the mean [SEM]; range 240 to 560 mg/day). Selective coronary arteriography in 26 patients revealed significant obstructive coronary artery disease (70% or greater luminal diameter narrowing) in 10, whereas the remaining 16 had coronary arterial spasm superimposed on angiographically normal coronary arteries. In addition to placebo or verapamil, 15 patients were maintained throughout the study on a stable dose of oral isosorbide dinitrate (104 ± 17 mg/day in 4 to 6 divided doses); in each patient, this dose was held constant throughout all treatment periods.

Individuals with any of the following were excluded from the study: (1) underlying diseases, including congestive heart failure, uncontrolled systemic arterial hypertension, hypotension, associated valvular or congenital cardiac disease, sick sinus syndrome, insulin-dependent diabetes mellitus, renal or hepatic disease, or any terminal illness; (2) certain electrocardiographic abnormalities (left bundle branch block, severe bradycardia, 2nd or 3rd degree atrioventricular block, atrial flutter or fibrillation, or preexcitation syndrome); or (3) the concomitant administration of disopyramide or beta-adrenergic blocking agents.

After a diagnosis of variant angina was established and informed consent was obtained, each patient received open-label verapamil for one month, during which time the dose of the drug was advanced upwards, so as to achieve an optimal effect without adverse effects. Subsequently, each patient was randomly and blindly assigned to 1 of 2 groups for the next 8 months: four 2 month blocks of placebo alternating with verapamil. If frequent rest angina was accompanied by electrocardiographic evidence of ischemia and required hospitalization, the patient was blindly advanced to the next therapy. During the 8 months of blinded therapy, several variables were assessed: (1) number of episodes of chest pain per week, (2) number of nitroglycerin tablets used per week, and (3) number of adverse effects, all recorded daily by the patient in a diary; (4) number of hospitalizations required for severe chest pain; and (5) number of episodes of transient S-T segment deviation (elevation or depression of 0.1 mV or greater) on weekly 24 hour 2-channel ambulatory electrocardiographic monitoring; analysis of the Holter monitor recordings was performed as described previously.[18]

All variables were analyzed without knowledge of the order in which placebo and verapamil were administered. For each variable, the 4 months of placebo therapy were averaged and compared with the average of the 4 months of verapamil therapy with a paired t test and Wilcoxon matched-pairs signed ranks test. All values were reported as mean ± SEM. For all analyses, a p value less than 0.05 was considered significant.

Comparison of verapamil and nifedipine: clinical efficacy: The first 23 patients to complete the long-term comparison of placebo and verapamil (just described) were enrolled in an additional 2 months of nifedipine therapy. During these 2 months, nifedipine was administered as an open-label medication (that is, neither blinded nor randomized) in the maximally tolerated dose (71 ± 5 mg/day in 3 to 4 equal doses; range, 40 to 160 mg/day). Thus, in all 23 patients, both verapamil and nifedipine were administered in dosages that afforded maximal relief of angina without limiting adverse effects. In addition to placebo, verapamil, or nifedipine, 14 patients were treated with a stable dose of oral isosorbide dinitrate which was unchanged throughout the 3 treatment periods (116 ± 18 mg/day in 4 to 6 divided doses; range, 40 to 200 mg/day). During this additional 2 month period of nifedipine therapy, the variables assessed during the long-term comparison of placebo and verapamil were similarly measured.

For the purpose of data analysis, each variable was quantitated during the latter 4 months of blinded therapy (2 months of placebo, 2 months of verapamil) as well as the 2 months of nifedipine therapy. A repeated measures analysis of variance was performed for each variable to determine if some groups were different from others, after which the Newman-Keuls multiple comparison procedure was performed. The Friedman chi-square nonparametric test[19] was also used to evaluate each variable, after which nonparametric multiple comparisons were performed. When the effects of nonnormality were sufficient to cause disagreement between parametric and nonparametric procedures, results of the nonparametric analysis were reported. All values were expressed as mean ± standard error; a p value of 0.05 or less was considered significant.

Comparison of verapamil and nifedipine: effects on left ventricular function: During the final week of the last 3 of the five 2-month treatment periods (that is, at the end of months 6, 8, and 10), 10 of the patients underwent equilibrium gated blood pool scintigraphy at rest and during supine bicycle exercise. All exercise studies were performed 1 to 2 hours after a regularly scheduled dose of medication (placebo, verapamil, or nifedipine). Multigated equilibrium blood pool imaging was performed after in vivo labeling of red blood cells with 30 mCi of technetium-99m sodium pertechnetate, according to the technique previously described.[20,21] Data collection was performed with a portable gamma scintillation camera (Ohio Nuclear VIP-450). Resting and exercise gated blood pool scintigrams were obtained in a modified left anterior oblique projection; the angle of obliquity was adjusted to allow the clearest separation between the ventricles while minimizing the interventricular septal thickness. Resting images were acquired for (1) a predetermined number of cardiac cycles, so that the total acquisition time was 5 to 8 minutes; (2) 32 frames/cardiac cycle; and (3) 100% of the cardiac cycle. The result was a minimum of 150,000 counts/frame of the study.

Each subject's feet were elevated and attached to the bicycle pedals before beginning the exercise study. After a 3 minute equilibration period, an additional resting scintigram was obtained to assess the effect of leg elevation on the variables measured. These and subsequent exercise images were acquired for (1) a predetermined number of cardiac cycles, so that the total acquisition time during exercise was 3 minutes; (2) 32 frames/cardiac cycle; and (3) 100% of the cardiac cycle. This provided a minimum of 100,000 counts per frame during

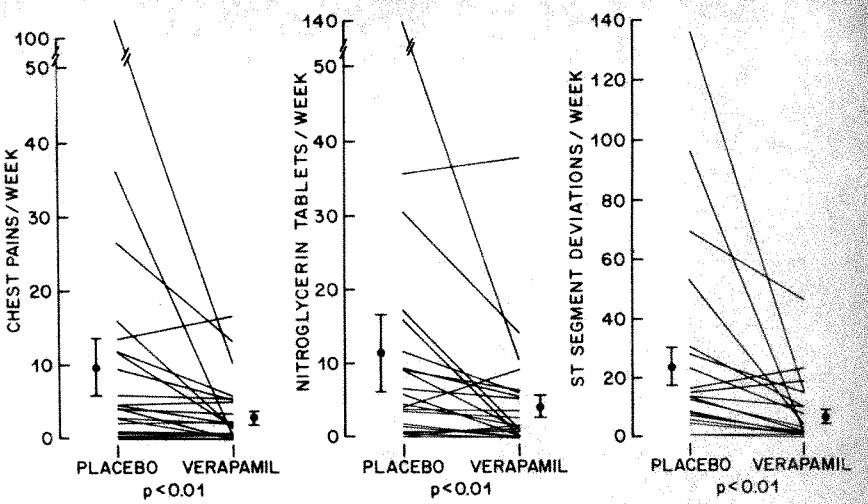

FIGURE 1. The number of anginal episodes per week (**left panel**), the number of nitroglycerin tablets used per week (**middle panel**) and the number of transient S-T segment deviations per week by 2 channel ambulatory electrocardiographic monitoring (**right panel**) during 4 months of placebo therapy and 4 months of treatment with verapamil in 27 patients with Prinzmetal's variant angina. **Each line** represents the data from one patient, and the means ± SEM are displayed on either side of each set of lines. In comparison with placebo, verapamil reduced the frequency of all 3 variables.

exercise. Imaging was performed at each work load, beginning at 150 kilopond-meters per minute (kpm/min) and continuing until the termination of the test. At the beginning of the 1st and each subsequent work load, the subject exercised for 1 minute before beginning the 3 minute imaging period, which allowed the heart rate to reach a new steady level and uninterrupted gating to occur. During acquisition of scintigraphic data, heart rate did not vary by more than 15% of the value recorded at the start of the acquisition period. The Frank lead system or a truncal 12 lead system was used for electrocardiographic monitoring, and the blood pressure was recorded by auscultation at rest and during each work load. Left ventricular volumes and ejection fraction were determined with a nongeometric technique developed and validated in our laboratory[22,23] and in others.[24]

During each of the three exercise studies, the maximal achieved work load was determined. Both at rest and during the maximal work load common to all 3 exercise studies, the following variables were analyzed: heart rate, systolic blood pressure, left ventricular end-diastolic volume index, left ventricular end-systolic volume index, and left ventricular ejection fraction. For each variable (at rest and during exercise), a repeated measures analysis of variance was performed to determine if 2 or more groups were different from one another, after which the groups were compared using the Newman-Keuls mutiple comparison procedure.[18,19] When changes from rest to exercise were assessed for one of the 3 agents, the paired t test was employed. A probability (p) value of less than 0.05 was considered significant.

Results

Long-term, randomized, double-blinded comparison of placebo and verapamil in patients with variant angina: During verapamil administration, the frequency of chest pain, nitroglycerin utilization, and transient S-T segment deviations by ambulatory electrocardiographic monitoring decreased in comparison with the effects of the placebo (Fig. 1). During verapamil therapy, 1 patient died, but none required hospitalization for clinical instability. In contrast, during placebo therapy, 7 patients had at least one episode of clinical instability requiring hospitalization or a blind advancement in medication sequence ($p < 0.025$). In each case, an advancement to verapamil therapy resulted in relief of symptoms.

Comparison of verapamil and nifedipine: clinical efficacy: During therapy with both verapamil and nifedipine, the frequency of angina was reduced in comparison with that during placebo (Fig. 2). Similarly, nitroglycerin consumption and the number of episodes of transient S-T segment deviation on calibrated 2 channel ambulatory electrocardiographic monitoring were less during therapy with verapamil and nifedipine than during placebo (Fig. 2).

During placebo therapy, 7 of the 23 patients required hospitalization because of severe angina; 2 patients required hospitalization for chest pain during nifedipine therapy ($p = 0.06$ in comparison with placebo), and no patient was hospitalized during treatment with verapamil ($p < 0.01$ in comparison with placebo). No patient had myocardial infarction or died.

Comparison of placebo, verapamil, and nifedipine: adverse effects: adverse reactions were observed during long-term placebo, verapamil, and nifedipine therapy that were not noted during the initial dose titration phase for each agent. During long-term therapy with placebo, 1 patient reported constipation and 1 developed abdominal distention. During long-term verapamil administration, 1 patient had palpitations (in conjunction with an accelerated atrioventricular nodal rhythm on ambulatory electrocardiographic monitoring), 2 had asymptomatic prolongation of the P-R interval (>0.20 seconds), and 5 had constipation. None of these forced a discontinuation or reduction in the dosage of verapamil in any patient. During long-term nifedipine therapy, 10 patients had adverse effects. One patient had headache and orthostatic hypotension which forced a premature termination of nifedipine. In 2 patients headache and nonorthostatic dizziness developed which mandated a discontinuation of nifedipine after 1 month. Seven others had dose-limiting adverse effects, including orthostatic hypotension in 2, pedal edema in 1, nausea, anorexia, and nonorthostatic dizziness in 3, and headache in 1.

Comparison of verapamil and nifedipine: effects on left ventricular function (Table I): Resting heart rate was lower during verapamil therapy than during treatment with nifedipine, but resting systolic arterial pressure was similar during treatment with placebo and both active drugs. The maximal work load achieved by each patient was similar during the 3 treatment periods; at this maximal work load, heart rate and systolic arterial pressure increased during treatment with all 3 agents, but remained lower during verapamil therapy compared with the placebo. Resting left ventricular end-diastolic volume index, end-systolic volume index, and ejection fraction did not differ significantly among the 3 treatment periods; at the maximal common work load, ejection fraction increased to a similar degree during therapy with all agents (Table I, Fig. 3).

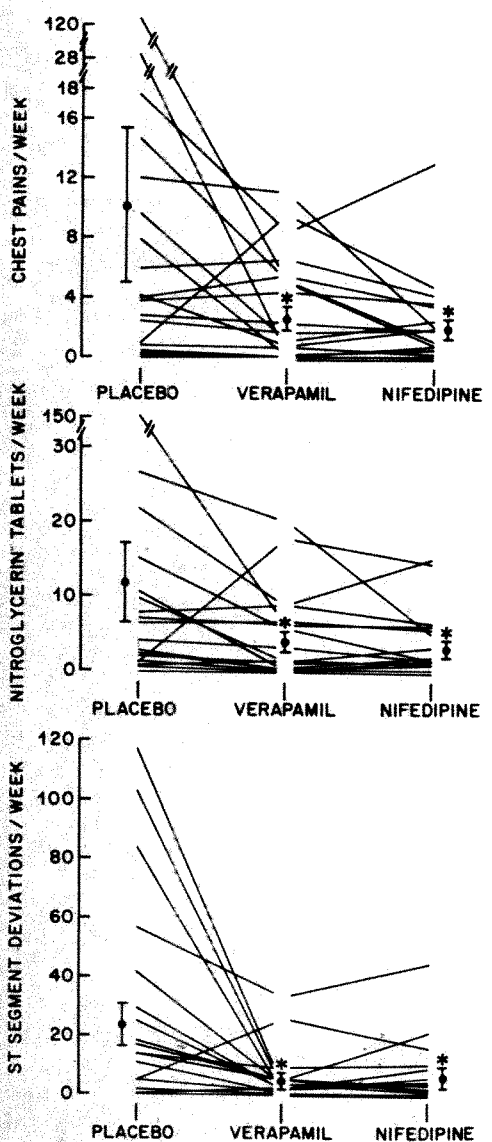

FIGURE 2. Number of anginal episodes per week (**top panel**), nitroglycerin tablets consumed per week (**middle panel**), and transient S-T segment deviations by 2 channel ambulatory electrocardiographic monitoring (**lower panel**) during placebo (**left**), verapamil (**middle**), and nifedipine (**right**) in 23 patients with variant angina pectoris. **Each line** represents the data from one patient, and the means ± SEM are shown for each treatment period. In comparison with placebo, both verapamil and nifedipine reduced the frequency of all 3 variables, and there was no difference between the two drugs. **Asterisks** indicate $p < 0.05$ in comparison with placebo.

Discussion

Over the past two decades, a group of pharmacologic agents known as the calcium antagonists has been used outside the United States for the treatment of several forms of ischemic heart disease, including Prinzmetal's variant angina. Preliminary observations have shown that these agents are effective in this syndrome,[3–9,25,26] but few studies have assessed the utility of these drugs in a randomized, controlled, and blind fashion or have compared the different calcium antagonists with one another. The studies described herein demonstrate that verapamil is safe and effective in the long-term management of patients with variant angina and that it is similar in efficacy to nifedipine in the therapy of these patients.

Verapamil versus placebo in patients with Prinzmetal's variant angina: Since its introduction in Europe in 1962, verapamil has been used for the treatment of patients with supraventricular tachyarrhythmias,[27,28] essential systemic hypertension, hypertrophic cardiomyopathy,[29,30] and several forms of coronary heart disease. Previous uncontrolled studies have suggested that verapamil is beneficial in patients with Prinzmetal's variant angina pectoris,[3–6] the clinical syndrome of chest pain and concomitant S-T segment elevation due to coronary arterial spasm.[31] The present randomized, blind, and long-term evaluation demonstrates verapamil's efficacy in patients with this disease. In comparison with placebo, verapamil reduced the

TABLE I Hemodynamic and Scintigraphic Variables at Rest and During Exercise During Therapy With Placebo, Verapamil, and Nifedipine (Each Administered for 2 Months)

Variable	Placebo	Verapamil	Nifedipine
Maximal work load achieved (kpm/min)	360 ± 40	358 ± 31	355 ± 43
HR (beats/min)			
Resting	77 ± 4	72 ± 3*	80 ± 3
Exercise	127 ± 3†	118 ± 3†‡	127 ± 3†
SBP (mm Hg)			
Resting	133 ± 8	130 ± 5	128 ± 7
Exercise	187 ± 7†	170 ± 4†§	174 ± 6†
LVEDVI (ml/m^2)			
Resting	70 ± 8	78 ± 11	82 ± 14
Exercise	73 ± 7	87 ± 12†	87 ± 17
LVESVI (ml/m^2)			
Resting	30 ± 8	31 ± 9	38 ± 11
Exercise	26 ± 8†	30 ± 9	33 ± 15
LVEF			
Resting	0.61 ± 0.05	0.65 ± 0.05	0.60 ± 0.04
Exercise	0.69 ± 0.06†	0.71 ± 0.04†	0.71 ± 0.06†

* $p < 0.05$ in comparison with nifedipine. † $p < 0.05$ in comparison with the same pharmacologic agent at rest. ‡ $p < 0.05$ in comparison with both placebo and nifedipine. § $p < 0.05$ in comparison with placebo.

All figures are mean ± standard error of the mean. HR = heart rate; kpm/min = kilopondmeters/minute; LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index.

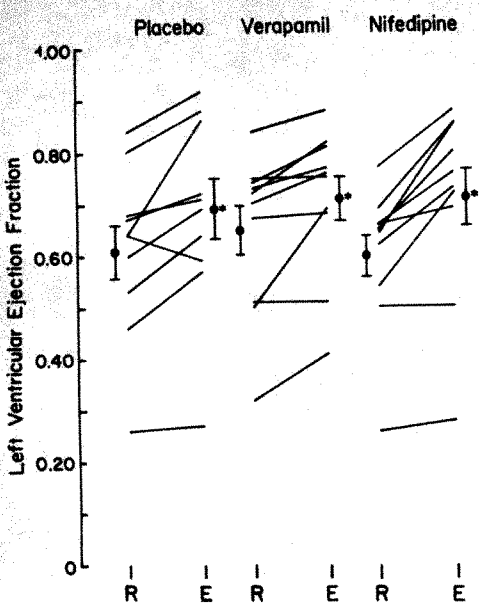

FIGURE 3. Left ventricular ejection fraction at rest (R) and at the maximal work load common to all 3 exercise studies (E) for the 3 therapy periods. **Each line** represents the data from one patient, and the mean values ± SEM are depicted on either side of the lines. At rest and during exercise, values during the 3 treatment periods were similar. **Asterisks** indicate $p < 0.05$ when compared with the same pharmacologic agent at rest.

frequency of both anginal episodes and nitroglycerin utilization, decreased the number of episodes of clinical instability requiring hospitalization, and reduced the frequency of transient S-T segment deviations, as detected by 2 channel ambulatory electrocardiographic monitoring. Furthermore, verapamil was well tolerated; adverse effects were relatively minor and did not limit its administration.

Verapamil versus nifedipine in patients with Prinzmetal's variant angina: clinical efficacy: Because of its dilator actions on systemic and coronary arteries, nifedipine has been used to treat systemic hypertension,[32] angina of effort,[33,34] angina at rest,[35] and variant angina.[7–9] It has also been used (in a limited manner) as a myocardial "protectant" during cardiopulmonary bypass.[36]

The present study demonstrates that verapamil and nifedipine are of similar efficacy in patients with variant angina pectoris. Both agents reduced the frequency of angina and nitroglycerin utilization, and both drugs diminished the frequency of transient ischemic S-T segment alterations by calibrated 2 channel ambulatory electrocardiographic monitoring. However, adverse effects occurred more frequently with nifedipine than with verapamil. In 10 of the 23 patients who received both drugs, adverse reactions limited the amount of nifedipine that could be administered; in contrast, side effects during verapamil administration were relatively minor and did not alter the dosage.

This comparison of verapamil and nifedipine in patients with variant angina has certain limitations. Although placebo and verapamil were administered as part of a randomized and double-blind evaluation, nifedipine was administered as an "open-label" medication; hence, investigator and patient bias may have influenced our results in favor of nifedipine. Furthermore, whereas verapamil and placebo therapies were compared in random order, verapamil and nifedipine were not so compared; the cyclic nature of ischemic episodes in variant angina may have led to a spontaneous decrease in the number of ischemic episodes recorded during the latter phases of this study, and thus would have favored our finding a favorable result with nifedipine. Further studies will require the blind administration of all 3 pharmacologic agents with placebo periods before and after the administration of each active drug. With these limitations in mind, this study shows that verapamil and nifedipine are highly beneficial and are of similar efficacy in the therapy of patients with variant angina. Thus, the availability of both calcium antagonists makes it possible for each patient with variant angina to receive the drug optimally suited for his specific needs. If he cannot tolerate one of them, the other can be administered and a similar salutary effect anticipated.

Verapamil versus nifedipine in patients with Prinzmetal's variant angina: effects on left ventricular function: Because verapamil diminishes the rate of spontaneous impulse initiation by the sinoatrial node[37] as well as the rate of conduction through atrioventricular tissue,[38] it is extremely effective in the therapy of supraventricular tachyarrhythmias[39,40]; in contrast, nifedipine exerts no discernible effects on the cardiac conduction system. Although both drugs possess direct negative inotropic effects in vitro,[10,11] the peripheral vasodilator actions of verapamil and nifedipine offset these negative inotropic effects in man.[14,15] Neutralization of these cardiodepressant effects by peripheral vasodilation is thought to be more complete with nifedipine[17]; hence, nifedipine is frequently regarded as exerting less overall negative effects on cardiac performance. However, this presumption has largely been based on the acute effects of rather large doses given parenterally. Previous studies have not compared the effects of the *long-term oral* administration of verapamil and nifedipine on left ventricular performance in the same patients.

In the present study we compared the effects of long-term therapy with placebo, verapamil, and nifedipine on left ventricular performance in 10 patients with variant angina. Left ventricular volumes and ejection fraction were similar during the 3 treatment periods both at rest and during exercise, even in the 2 patients with depressed left ventricular performance. Therefore, although previous studies showed that high concentrations of intravenously administered verapamil exert a substantial negative inotropic effect in animal studies,[41] this study demonstrates that long-term, orally administered verapamil does not adversely affect left ventricular performance either at rest or during exercise.

Of the 10 patients comprising this study, 8 had resting left ventricular ejection fractions during placebo therapy above 0.50, whereas in the remaining 2 the resting

ejection fractions on placebo were 0.46 and 0.26. Neither patient manifested symptoms or signs of left ventricular failure. Both tolerated verapamil without difficulty, and, in fact, their resting left ventricular ejection fractions increased to 0.51 and 0.32, respectively. Similarly, nifedipine was administered to both without problems, and the resting ejection fractions during this therapy were 0.50 and 0.26, respectively. Thus, neither verapamil nor nifedipine caused a worsening of left ventricular performance even in the 2 patients with a substantial depression of ejection fraction. Although these results are encouraging, they should be extrapolated cautiously to a larger group of patients with depressed left ventricular performance, especially those who manifest evidence of left ventricular failure.

Acknowledgment

We acknowledge the secretarial assistance of Juanita Alexander.

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Verapamil Therapy for Unstable Angina Pectoris: Review of Double-Blind Placebo-Controlled Randomized Clinical Trials

JAWAHAR MEHTA, MD and C. RICHARD CONTI, MD

The effectiveness of verapamil in the management of patients with unstable angina pectoris associated with obstructive coronary artery disease was evaluated in 2 double-blind placebo-controlled randomized clinical trials. In the 1st study, verapamil was compared with placebo using alternating 48 hour treatment periods in a multiple cross-over protocol. Verapamil was superior to placebo in abolishing symptomatic and asymptomatic ischemic episodes; there were 127 ischemic events during treatment with placebo but only 27 episodes during therapy with verapamil ($p < 0.006$). In the 2nd study, verapamil and placebo were compared using a double-blind randomized parallel design in which the choice of drug was altered and the doses administered were increased according to the individual responses. Verapamil reduced anginal attacks in 12 of 13 patients, but placebo was effective in only 1 of 6 ($p < 0.025$); verapamil reduced daily anginal attacks from 3.2 to 0.6/day ($p < 0.01$). Thus, verapamil is highly effective in the short-term management of patients with unstable angina secondary to coronary artery disease.

The management of patients with unstable angina pectoris continues to be a difficult clinical problem.[1] Although the choice between initial surgical and medical therapy appears to favor a nonsurgical approach, continued controversy surrounds the choice of medical treatment regimens.

A rational approach to the management of patients with unstable angina should be based on an understanding of the pathogenesis of the syndrome. Because many patients with unstable angina have little or no change in blood pressure and heart rate at the onset of their symptoms,[2] coronary artery spasm and in vivo platelet aggregation are important mechanisms by which the magnitude of fixed obstruction secondary to coronary atherosclerosis may be transiently exacerbated.[3] Decreased oxygen supply rather than increased demand may be the primary pathogenetic mechanism of myocardial ischemia in patients with unstable angina[4]; hence, treatment of such patients with beta-adrenergic blocking agents has been questioned, because these agents may have deleterious effects in patients with coronary artery spasm.[5] Nitrates exert beneficial effects on both myocardial oxygen demand and supply[6–8] and hence are widely used in the treatment of unstable angina[9]; however, many patients fail to respond to nitrates alone, experience prohibitive adverse reactions, or find them inconvenient for long-term therapy.

The class of drugs known as the calcium antagonists possess a number of pharmacologic properties that may be beneficial in patients with angina pectoris at rest or on exertion. These drugs are potent systemic vasodilator agents and act either directly by blocking the entry of calcium into vascular smooth muscle[10] or indirectly by a sympatholytic effect[11,12]; this systemic vasodilation should reduce myocardial oxygen requirements at any given level of work.[13] In addition, these agents may specifically act on dynamic factors in the coronary circulation, which predispose to vasospasm; this action may be accomplished by direct antagonism of spontaneous smooth muscle contraction[14] or indirectly by inhibition of platelet aggregation[15–17] and of thromboxane A_2 synthesis (unpublished observations). Accordingly, several recent trials of slow channel calcium antagonists have produced encouraging results in patients with exertional and variant angina[18–23]; recent studies indicate that these agents may also be beneficial in patients with unstable angina.[24–27]

The purpose of this report is to review the clinical effectiveness of one of these calcium antagonists, verapamil, in the short-term management of patients with unstable angina associated with obstructive coronary artery disease.

Double-Blind Multiple Cross-Over Trial in Unstable Angina

In 1979 Parodi et al.[24] reported the 1st placebo-controlled trial of verapamil in patients with unstable angina.

Patients: These investigators evaluated 12 patients (aged 34 to 70 years, mean 54), 7 of whom had both exertional and rest angina, whereas 5 had only rest angina with normal exercise tolerance. The electrocardiogram during the ischemic event revealed S-T segment ele-

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vation in 6, depression in 4, and alternate elevation and depression in the same lead in the remaining 2 patients. A massive reduction of myocardial perfusion during a spontaneous angina attack was documented in all 8 patients in whom thallium-201 was injected at the beginning of an ischemic episode. Coronary angiography was performed in 9 patients and showed significant obstructive coronary artery disease (greater than 50% coronary luminal narrowing) in 8.

Protocol design: The study protocol consisted of a 2 day run-in period while patients received diazepam, followed by four 2 day treatment periods consisting of either placebo or verapamil (480 mg daily) in alternating randomized fashion. The efficacy of therapy was determined by quantitating symptomatic and asymptomatic episodes of S-T segment depression or elevation during continuous electrocardiographic monitoring.

Results: For the group of patients as a whole, the number of S-T segment shifts in the placebo run-in period and the 2 placebo periods was the same (128 versus 123 and 130 events, respectively). In contrast, during each period of verapamil treatment, a highly significant reduction in the number of episodes to 31 and 23 events was observed ($p < 0.006$). This reduction was similar in the number of episodes of S-T segment elevation or depression and of symptomatic and asymptomatic episodes (Fig. 1). In 2 patients, ischemic episodes were totally abolished during both verapamil treatment periods; in another 4 patients, verapamil therapy eliminated ischemic episodes entirely in 1 of the 2 treatment periods.

Side effects: The investigators reported muscle cramps and weakness, constipation, and transient mental confusion in one patient each during verapamil therapy. There were no significant effects on heart rate or blood pressure. The electrocardiographic P-R interval increased in 7 of 12 patients given verapamil, but first degree atrioventricular block (P-R interval greater than 0.20 second) developed in only 3 patients.

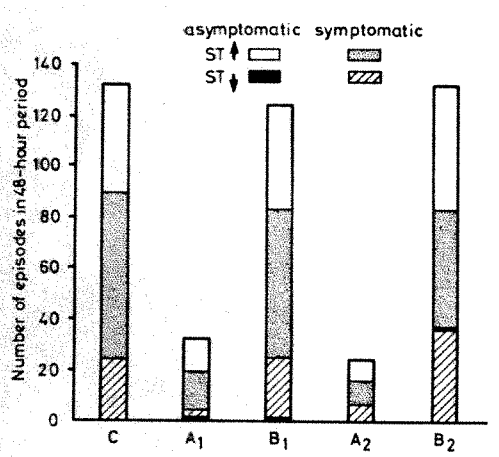

FIGURE 1. The total number of episodes in 12 patients in each 48 hour period of the trial. C indicates run-in period; A_1, A_2 = verapamil periods; B_1, B_2 = placebo periods. Control and placebo periods show similar number and type of ischemic episodes, whereas during treatment with verapamil there is a conspicuous reduction in frequency of all types of episodes. (Reproduced, with permission, from Parodi et al.[24])

Double-Blind Parallel Randomized Trial in Unstable Angina

Mehta et al.[25] in 1981 reported another placebo-controlled trial of verapamil in patients with unstable angina.

Patient population: These investigators evaluated 15 patients (out of 65 patients screened), who were experiencing angina at rest with at least 2 episodes of chest pain per 24 hours associated with S-T segment changes; patients with congestive heart failure, hypotension, and conduction system disease were excluded. Fourteen men and 1 woman (aged 42 to 80 years, mean 61) entered the study. Five patients had received prior therapy with beta-blocking drugs and all had received nitrates. Duration of angina before this study was 2 weeks to 11 years. In the preceding month, all patients had episodes of rest angina (range 1 to 30 per week), and 13 also had exertional angina (range 1 to 50 attacks per week). Twelve of the 15 patients had coronary angiography, and all had significant (greater than 50% narrowing) 2- or 3-vessel disease; 1 patient also had 60% luminal narrowing of the left main coronary artery.

Protocol design: All patients entered a single-blind placebo run-in period that lasted 24 hours, after which patients who continued to meet the criteria for the study were randomized to receive either placebo or verapamil (320 mg/day) in a double-blind fashion for the 2nd 24 hour period. At the end of the 2nd day, patients who were considered "responders" (defined as those having a 50% or greater reduction in the frequency of symptomatic rest angina) continued to take the same medication; patients who did not respond were crossed to receive verapamil: a nonresponder to placebo received verapamil 320 mg daily, whereas a nonresponder to verapamil (320 mg daily) was advanced to a dose of 480 mg daily. At the end of the 3rd day, a similar assessment of response was made; responders continued to take their "effective" drug, whereas nonresponders were crossed to low-dose verapamil (320 mg daily) or had their dose of verapamil increased (480 mg daily), as just discussed. The study was unblinded at the end of the 4th 24 hour period. Patients stayed on bedrest for the entire duration of the study. Sublingual nitroglycerin was permitted for relief of symptomatic ischemic episodes.

Results: During the 1st 24 hour single-blind placebo period, the frequency of angina episodes ranged from 2 to 8 (mean 3.2) and the number of nitroglycerin tablets consumed ranged from 0 to 9 (mean 3.1). With chest pain, 11 patients had S-T segment depression, 1 elevation, and the remaining 3 alternate depression and elevation in the same leads.

In the 2nd 24 hour period, 6 patients received placebo and the other 9 verapamil (Fig. 2). Only 1 of the 6 patients treated with placebo improved, whereas 7 of the 9 patients randomized to verapamil (320 mg daily) responded to therapy ($p < 0.025$ by Fisher's exact test); 1 patient failed to improve, and 1 patient developed evidence of myocardial necrosis which began before verapamil administration, and so was excluded from further

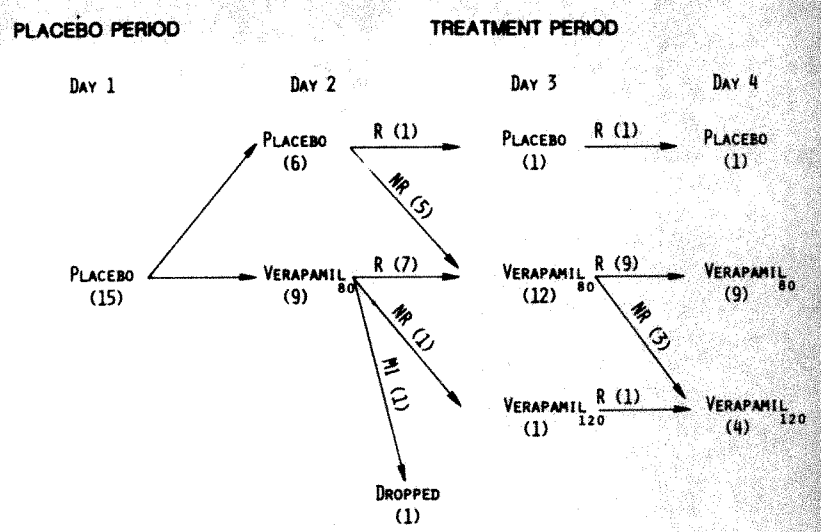

FIGURE 2. A summary of the protocol, treatment schedule, and response to therapy in 15 patients with rest angina. Verapamil 80 and 120 = 80 mg or 120 mg every 6 hours; R = responder; NR = nonresponder. At the end of day 4, there were 13 patients on verapamil and 1 on placebo. (Reproduced, with permission, from Mehta et al.[25])

study. The 5 patients who failed to respond to placebo were then treated with verapamil (320 mg daily), whereas the 1 patient who failed to respond to verapamil was advanced to large doses of verapamil (480 mg/day).

In the 3rd 24 hour period, the 1 placebo-responder continued to respond. Of the 13 patients on verapamil, 10 were responders and 3 nonresponders, and these were advanced to large doses of verapamil (480 mg/day) (Fig. 2).

In the 4th 24 hour period, 1 patient receiving placebo continued to respond (Fig. 2). Of the 13 patients receiving verapamil (320 mg/day in 9 patients and 480 mg/day in 4), all except 1 patient were responders to the drug; the latter patient received only 320 mg of verapamil daily. At the end of this short-term study, frequency of chest pain had decreased from 3.2 to 0.6 episodes per day, and nitroglycerin consumption had declined from 3.1 to 0.3 tablets per day ($p < 0.01$) compared with the 1st 24 hour placebo run-in period.

Side effects: Verapamil therapy was well tolerated with few side effects. There were no hematologic adverse effects or alterations in renal or hepatic function. Electrocardiographic P-R interval prolongation was noted in 2 patients; one of these had a decrease in the P-R interval when the dose of verapamil was decreased to 240 mg/day but still had sustained relief of anginal symptoms.

Discussion

Recent investigators have indicated that patients with variant and unstable angina at rest commonly exhibit dynamic alterations in their coronary circulation, which when superimposed on partially obstructive atherosclerotic lesions can result in a primary reduction in myocardial blood flow. Such dynamic factors include coronary artery vasospasm, in vivo platelet aggregation, and enhanced platelet prostaglandin generation.[28–30] Calcium channel blocking agents, such as verapamil, can abolish vasospasm, inhibit in vivo platelet aggregation, and block the synthesis of thromboxane A_2, and thereby antagonize specifically those dynamic factors that are critical in the pathogenesis of the unstable angina syndrome.

Necessity for placebo-controlled trials in unstable angina: Although a number of calcium-blocking agents have been effective in patients with angina at rest, these trials were largely uncontrolled and treated patients with variant angina and normal coronary arteries[21,22]; few trials have involved placebo-treated controls in patients with severe obstructive coronary artery disease and unstable angina pectoris.[24–27] Because there is a considerable variability in the clinical course of patients with unstable angina,[31–33] the use of placebo-controlled double-blind trials is essential in determining efficacy of any new pharmacologic approach. The specialized environment of the coronary care unit by itself may influence the frequency of chest pain in these patients; this finding was evident in that only 15 of 65 patients with a history of unstable angina on admission in the short-term study of Mehta et al.[25] continued to experience episodes of rest angina after treatment with placebo for 24 hours, and thus qualified for eligibility into the study. Robertson et al.[34] also demonstrated that patients with variant or vasotonic angina frequently become symptom-free soon after admission to the hospital. The differences in the magnitude of physical and emotional stress between ambulatory outpatient and inhospital phases may have a bearing on these differences in the frequency of angina. These facts clearly emphasize the need for the use of placebo in determining the efficacy of a drug in relieving symptomatic as well as asymptomatic episodes of myocardial ischemia.

Evidence for effectiveness of verapamil: The two placebo-controlled randomized clinical trials reviewed in this report thus take on particular significance. All patients in both studies had subjective and objective evidence of myocardial ischemia characterized by chest pain and S-T segment changes; most patients also experienced asymptomatic episodes characterized by similar S-T segment changes without chest pain. Before

hospitalization, most patients had a history of exertional as well as rest angina; this angina proved to be secondary to obstructive coronary artery disease in nearly all of the patients evaluated by cardiac catheterization. Verapamil was administered in a double-blind randomized fashion using two different study protocols: the 1st study involved multiple cross-overs from placebo to verapamil and from verapamil to placebo; the 2nd study involved initial randomization followed by cross-over from placebo to verapamil and advancement from a small to a large dose of verapamil. Regardless of the protocol design, both studies indicated that verapamil markedly reduces the frequency of asymptomatic and symptomatic ischemic events in over 90% of all patients with unstable angina.

The beneficial effects of verapamil in patients with unstable angina pectoris evident in these two studies are similar to those reported by Gerstenblith and colleagues with the use of nifedipine.[26] However, important differences between the verapamil and nifedipine trials should be noted. The studies by Parodi et al.[24] and Mehta et al.[25] showed that verapamil therapy provided *short-term symptomatic* benefits in patients with unstable angina with either S-T segment depression or elevation, or both. The Gerstenblith trial did not evaluate the immediate relief of symptoms, but treated patients for 4 months in order to assess the effect of nifedipine on the frequency of failure of medical therapy. Patients randomized to nifedipine were less likely to require surgery for relief of angina than those randomized to placebo; the incidence of sudden death and myocardial infarction was similar in the 2 groups. However, this favorable effect of nifedipine was noted only in those patients with unstable angina who had S-T segment elevations during episodes of rest pain; these findings contrast with those in patients treated with verapamil who were reported improved, regardless of the directional change in the S-T segment during the anginal event. Whether this indicates a real difference in effectiveness between the two drugs in patients with S-T segment depression during episodes of rest angina remains to be determined. Clinical results with *long-term* verapamil administration in patients with unstable angina pectoris, although not placebo-controlled, resemble those of the Gerstenblith study and are reported elsewhere in this symposium.[35]

In conclusion, verapamil therapy is markedly beneficial for the short-term prophylaxis and management of symptomatic and asymptomatic ischemia in patients with severe obstructive coronary artery disease and unstable angina at rest. The drug can produce a rapid stabilization of symptoms greater than can be provided by hospitalization, sedation, intensive observation, and bedrest alone without producing frequent or serious adverse reactions.

Acknowledgment

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Verapamil Versus Propranolol for Angina at Rest

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We previously showed that verapamil is highly effective in the treatment of patients with angina at rest, in whom coronary vasospasm likely represents the primary underlying pathophysiologic mechanism. Beta-adrenergic blocking drugs, on the other hand, do not exert any vasodilating effect on large coronary arteries, and hence do not represent a rational therapeutic approach to the treatment of patients with this syndrome.

The present report reviews the results of three clinical trials comparing the effectiveness of verapamil and propranolol in patients with angina at rest. In 17 patients enrolled in a randomized triple-crossover study, verapamil was superior to propranolol in preventing ergonovine-induced coronary artery spasm ($p < 0.001$). In 18 patients with rest angina evaluated in a double-blind crossover study, both verapamil and propranolol reduced the number of episodes of angina at rest (from 3.0/day to 1.7/day with propranolol, $p < 0.05$, and to 0.2/day with verapamil, $p < 0.001$); the degree of improvement with verapamil was superior to that seen with propranolol ($p < 0.005$). In 10 patients with rest angina evaluated in a single-blind multiple crossover trial which assessed symptomatic and asymptomatic ischemia, the number of ischemic events was reduced significantly only by verapamil (5 ± 1 episodes/48 hours) but not by placebo or propranolol (25 ± 3 and 23 ± 3 episodes/48 hours, respectively).

These studies confirm the effectiveness of verapamil in the management of patients with angina at rest; in contrast, the effectiveness of propranolol in this syndrome appears comparable to that of placebo.

Although propranolol is highly effective in the treatment of patients with angina of effort,[1–4] clinical studies in patients with angina at rest have largely been based on uncontrolled observations and have proved inconclusive.[5–11] The rationale for therapy with propranolol was based on an approach which considered the pathogenesis of chest pain at rest to be similar to that in patients with exertional symptoms. Recent studies, however, have emphasized that angina pectoris can be caused by multiple mechanisms[12] and that coronary vasospasm is responsible for ischemia in a significant proportion of patients with angina at rest.[13,14] Therefore, drugs such as propranolol that primarily reduce myocardial oxygen consumption but fail to exert vasodilating effects on the coronary vasculature may not be effective in patients in whom angina is caused by dynamic alterations in coronary luminal diameter rather than by an increase in myocardial metabolic demands.[15,16] In contrast, calcium channel antagonists can effectively block coronary vasospastic phenomena as well as reduce myocardial work, and controlled clinical trials have shown that these agents produce marked relief of symptoms in patients with angina at rest.[17–20] Among the drugs which have been evaluated, verapamil was the first to be utilized for the treatment of vasospastic coronary artery disease, and it remains our primary drug of choice for the management of patients with angina pectoris.

The present report reviews three objective clinical studies which have compared verapamil to propranolol in the treatment of the patient with angina at rest. The 1st study compares the effects of these drugs in the prevention of ergonovine-induced spasm in patients with variant angina without obstructive coronary artery disease. The second and third studies compare verapamil and propranolol in the short-term management of patients with unstable angina secondary to obstructive coronary artery disease hospitalized in the coronary care unit.

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Verapamil Versus Propranolol in Ergonovine-Induced Spasm

Bory et al.[21] investigated the effectiveness of verapamil and propranolol in 17 patients with variant angina without obstructive coronary artery disease.

Patients: All patients had episodes of chest pain at rest associated with characteristic electrocardiographic changes (S-T segment elevation in 12 cases, S-T segment depression in 2 cases, and T-wave inversion in 3 cases); all patients had coronary arteriographic confirmation of coronary artery spasm, which occurred either spontaneously or after provocation with ergonovine.

Trial design: After confirmation of the diagnosis, each patient entered a randomized triple crossover trial in which verapamil (360 mg daily), propranolol (120 mg daily), or placebo was administered for at least 3 days. At the end of each treatment period, ergonovine provocation was performed in each patient 3 hours after the last dose of the drug. Ergonovine was administered as an initial dose of 0.1 mg intravenously, followed by 0.2, 0.3, and 0.4 mg doses every 5 minutes until angina occurred. Treatment was considered completely effective if ergonovine administered in maximal doses failed to produce any symptoms or electrocardiographic changes; partly effective if the dose of ergonovine required to produce a positive response was larger than that needed during initial diagnostic cardiac catheterization; ineffective if the provoking dose of ergonovine was the same as during initial testing; and detrimental if the dose of ergonovine required to provoke ischemia was smaller than during initial provocation.

Results: The results of ergonovine testing are shown in Table I. The test became negative in 3 of 12 patients during treatment with placebo, in 4 of 15 patients during treatment with propranolol, and in 11 of 15 patients during treatment with verapamil; in the 4 patients who still had positive tests on verapamil, the dose of ergonovine required to provoke ischemia was higher than during initial testing. Whereas the responses to propranolol did not differ significantly from those seen during placebo therapy or during initial diagnostic evaluation, verapamil exerted a significant protective effect ($p < 0.001$).

Conclusions: Therefore, verapamil prevented ergonovine-induced spasm in most patients with variant angina, and the drug was superior in doing so to propranolol, which demonstrated little effectiveness in this study. Although the ergonovine test is highly sensitive and specific for variant angina[22,23] and correlates well with the active phase of the disease,[24] the results of this study must be interpreted cautiously. Because of the potential hazard of using ergonovine testing in patients with advanced coronary atherosclerosis, the investigators selected a population of patients with vasospastic angina and essentially normal coronary arteries; however, such patients represent only 7 to 10% of patients with angina pectoris,[12] and thus these results may not be applicable to the majority of patients with angina at rest, in whom coronary vasospasm is superimposed on organic coronary stenosis. Furthermore, it is possible that propranolol might exert favorable effects in patients with angina at rest (i.e., through metabolic alterations or changes in ventricular compliance) regardless of the importance of vasospasm in the specific population being evaluated. Finally, the dose of propranolol (120 mg daily) used in the study of Bory et al. was small and lower than that previously reported to be effective in patients with angina at rest. Therefore, no conclusions regarding the comparable effectiveness of verapamil and propranolol in patients with coronary artery lesions and angina at rest or mixed angina (resting and effort angina) can be drawn from this study.

TABLE I Results of Ergometric Testing Performed Before Therapy and After Treatment With Placebo, Propranolol, and Verapamil*

Patient	Before Treatment	Placebo	Propranolol	Verapamil
1	+0.2	+0.2	+0.2	+0.3
2	+0.1	+0.1	+0.1	−0.3
3	+0.2	+0.2	−0.3	−0.3
4	+0.1	+0.3	+0.3	−0.3
5	+0.1	NP	+0.1	+0.3
6	+0.3	NP	+0.2	NP
7	+0.2	+0.2	+0.3	−0.4
8	+0.2	NP	+0.2	+0.3
9	+0.3	+0.1	+0.1	−0.4
10	Spontaneous	+0.3	NP	−0.3
11	+0.2	−0.3	−0.3	−0.3
12	+0.2	+0.2	+0.2	−0.3
13	+0.2	−0.4	−0.4	NP
14	+0.4	−0.4	−0.4	−0.4
15	+0.2	NP	NP	−0.3
16	+0.4	+0.4	+0.4	−0.4
17	+0.2	NP	+0.2	+0.3

* Doses represent the maximal single dose administered. + indicates a positive test at the dose indicated in mg; − indicates a negative test; NP = not performed. (Reproduced, with permission, from Bory et al.[21])

Verapamil Versus Propranolol in Angina at Rest

Relief of Symptoms

In order to assess the relative effectiveness of propranolol and verapamil in reducing the number of anginal attacks in patients with coronary artery disease and angina at rest, Capucci et al.[25] performed a double-blind, randomized, crossover study comparing placebo, propranolol, and verapamil.

Patients and study design: Eighteen patients entered the study. All demonstrated 2 or more daily episodes of angina at rest associated with electrocardiographic S-T changes; 7 patients showed S-T segment elevation and 11 had S-T segment depression during anginal attacks. Thirteen of the 14 patients in the study who had coronary arteriography had severe obstructive coronary artery disease. The study design consisted of 5 treatment periods: a run-in period (2 days), placebo therapy (2 days), 1st drug (verapamil or propranolol for 4 days), placebo (1 day), and 2nd drug (propranolol or verapamil for 4 days). The dose of verapamil used was 480 mg daily, and the dose of propranolol used was 240 mg daily.

Results: The mean frequency of anginal attacks during the run-in period averaged 3.0 episodes per day and was unchanged by therapy with placebo (3.0 episodes during 1st placebo period and 2.3 episodes during the second placebo period). The number of episodes of angina decreased with propranolol to 1.7/day, significantly fewer than during the run-in and first placebo phases ($p < 0.05$), but not significantly different from the number during the 2nd placebo phase. Verapamil reduced the number of anginal attacks to 0.2/day, significantly fewer than during both placebo periods ($p < 0.001$) and significantly fewer than with propranolol ($p < 0.005$) (Fig. 1).

Conclusions: This study demonstrates that short-term therapy with verapamil is superior to propranolol and placebo therapy in reducing symptoms in patients with coronary artery disease, but these results must also be interpreted with caution. Since angina at rest is characterized by a spontaneous waxing and waning of symptoms, clinical trials of antianginal drugs must include frequent placebo periods in order to detect the possible spontaneous resolution of the disease.[18,26] Hence, the investigators in this study should have incorporated a short placebo period at the end of the trial (after the second drug period) in order to confirm persistence of the disease. In addition, the second placebo period may have been too short to permit adequate washout of the first drug, and thus may not serve as a valid point of comparison. Lastly and most importantly, objective assessment of ischemic episodes was lacking in this trial. Continuous electrocardiographic monitoring performed in patients with angina at rest[12,27] has established that most (50 to 70%) ischemic episodes in such patients are asymptomatic. Since the Capucci trial only assessed symptomatic episodes, the effect of each treatment on total ischemic attacks is unknown; hence, we can draw only limited conclusions concerning drug effectiveness.

Relief of Ischemia

In order to address some of the questions raised by the Capucci trial, Parodi et al.[28] recently completed a randomized single-blind crossover trial comparing the antianginal effects of propranolol and verapamil in patients with unstable angina at rest, hospitalized in a coronary care unit.

Patients: Ten consecutive patients with more than 2 anginal attacks at rest per day were enrolled in the trial; all attacks had confirmation of ischemia by simultaneous electrocardiographic changes. During the ischemic episodes, 3 patients showed S-T segment elevation, 2 S-T segment depression, and 5 S-T segment elevation or depression in different attacks. All but one patient had severe obstructive coronary artery disease by coronary arteriography.

Study design: The protocol began with a 2 day placebo run-in period followed by a 14 day single-blind protocol consisting of seven 48 hour treatment periods. Half of the patients received verapamil-placebo-propranolol-placebo-verapamil-placebo-propranolol; the other half received propranolol-placebo-verapamil-placebo-propranolol-placebo-verapamil. Hence, verapamil and propranolol were each administered for two 48 hour periods during the 2 week trial, and each of the active drug therapies was separated by a 48 hour placebo treatment period. Propranolol was given as 300 mg daily and verapamil as 400 mg daily. Prophylactic use of short- or long-acting nitrates was not allowed during the study; sublingual nitroglycerin was allowed only as treatment for anginal attacks. Oscilloscopic and Holter monitoring was performed throughout the trial in order to assess asymptomatic periods of ischemia.

A total of 1,582 episodes of symptomatic and asymptomatic ischemia were recorded during the trial, of which 685 (43%) were asymptomatic. The total number of ischemic episodes for each treatment period is shown in Figure 2. The mean number of events during the four placebo periods was 25 ± 3 attacks per 48 hours;

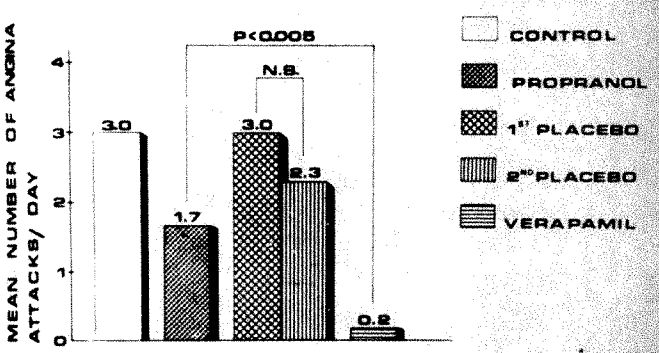

FIGURE 1. Overall results of a double-blind single crossover study of propranolol versus verapamil in 18 patients with unstable angina. (Reproduced, with permission, from Capucci et al.[25])

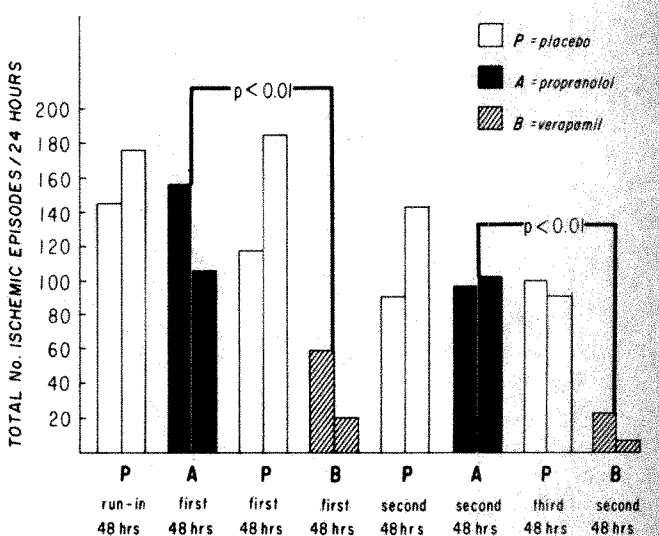

FIGURE 2. Overall results of a single-blind double crossover study in which propranolol (A) and verapamil (B) were compared in 10 patients with frequent ischemic attacks at rest. Every 48 hour period of treatment with each active drug is matched and compared with a 48 hour placebo period (P).

this was not significantly reduced during the 2 propranolol treatment periods (23 ± 3 episodes per 48 hours) but was reduced significantly during treatment with verapamil (5 ± 1 events per 48 hours) ($p < 0.01$ versus placebo and propranolol). Similarly, the number of nitroglycerin tablets consumed during placebo treatment (17 ± 2 tablets) was not significantly reduced by propranolol (14 ± 2 tablets) but was decreased by verapamil (2 ± 1 tablets) ($p < 0.01$). However, such averages mask a spontaneous decrease in the number of ischemic episodes noted during the performance of the trial; 312 episodes were noted during the first 48 hours of treatment with placebo, but the number decreased to 296, 229, and 184 events during the 2nd, 3rd, and 4th placebo periods ($p < 0.05$ between the 4th and 1st phases). A similar decrease in the number of ischemic events, however, was noted for the treatment periods (250 and 213 events for 1st and 2nd propranolol periods, respectively [$p > 0.10$]; 73 and 25 events during the 1st and 2nd verapamil periods, respectively [$p < 0.05$]).

The frequency pattern of ischemic attacks in two of the patients in the trial (Fig. 3) illustrates the importance of a multiple crossover protocol in assessing the effectiveness of drug therapy. If, in the patient shown in the left panel of Figure 3, the study had been stopped at the end of the first crossover period, propranolol and verapamil would have appeared to have a similar efficacy; the second half of the trial demonstrates, however, that only verapamil exerted a consistent and reproducible effect on the incidence of ischemic episodes. In the patient shown in the right panel of Figure 3, we observed a progressive reduction in the number of ischemic episodes throughout the trial; nevertheless, verapamil completely abolished the attacks during both 48 hour phases.

This is a preliminary report on the clinical results obtained during the trial. A complete analysis of the other results of the study (arrhythmias, magnitude and length of ischemic episodes, incidence and severity of asymptomatic versus symptomatic episodes as detected by Holter monitoring) is still in progress.

Conclusions and limitations: Although this trial does not support the use of propranolol in patients with angina at rest, such a conclusion should be interpreted cautiously. One of the 10 patients in this study had a reproducible decrease in ischemic episodes with propranolol comparable to that seen with verapamil; this suggests that propranolol may be effective in some patients with angina at rest. Furthermore, it is possible that doses higher than 300 mg of propranolol daily might have produced more marked beneficial responses than those seen in this study. Although the doses of propranolol used were sufficient to achieve beta-blockade and were comparable to those currently used in the management of patients with unstable angina, higher doses have been reported effective in reducing the incidence of ischemic episodes at rest.[29] Unfortunately, individual responses to propranolol vary widely, and thus the rather arbitrary choice of a dose of propranolol for purposes of comparison may bias any study against finding a beneficial effect of the drug.

Discussion

Effect of propranolol and verapamil on coronary spasm: Since coronary vasospasm has been shown to be a frequent cause of transient myocardial ischemic attacks at rest, drugs which have coronary spasmolytic effects should play a pivotal point in any rational therapeutic approach to patients with this syndrome. Although propranolol has long been used to treat patients with rest angina, beta-blockade results in significant constriction of large coronary vessels, an effect which is potentially detrimental in patients with unstable angina at rest.[30–32] In contrast, experimental and clinical studies[33–36] have demonstrated the potent vasodilating effect of verapamil on large coronary ar-

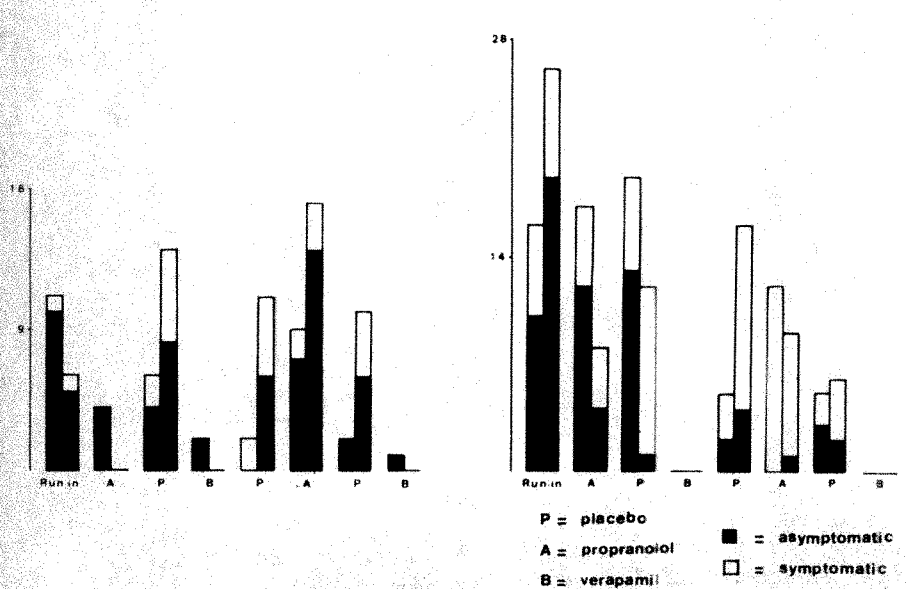

FIGURE 3. Histogram showing the incidence of ischemic episodes in Patients 1 (**left panel**) and 10 (**right panel**) with placebo (P), propranolol (A), and verapamil (B). The importance of using crossover periods in short-term trials in angina is illustrated in these two examples. See text for details.

teries; this vasodilation can be observed in man in both normal and atherosclerotic coronary segments and is comparable to that induced by nitroglycerin.[36] In addition, coronary vasospasm resolves after the intracoronary injection of verapamil.[37]

The results of Bory et al.[21] demonstrate that verapamil but not propranolol antagonizes the ability of ergonovine to provoke coronary vasospasm in patients with variant angina; the effectiveness of verapamil in such patients is in agreement with the observations of Waters et al.[38] No study has demonstrated a protective effect of propranolol in vasospastic disorders.

Verapamil versus propranolol in angina at rest: Both of the clinical trials reviewed herein indicate that verapamil is highly effective and superior to propranolol in the management of patients with unstable angina at rest.[25,28] These findings support previous controlled clinical trials comparing verapamil with placebo which demonstrated the value of calcium antagonists in the management of patients with coronary artery disease and symptoms at rest.[17,18]

In contrast to verapamil, propranolol was found to have little or no effect on the incidence of ischemic events at rest; this finding contradicts the favorable clinical experiences with propranolol in unstable angina reported by Papazoglov,[5] Mizgala,[6] Fischl,[7] Guazzi,[29] and their co-workers. Unfortunately, such experiences were largely uncontrolled and did not consider the natural course of the disease, since many patients with unstable angina have spontaneous remission of symptoms.[27,28] In the patients treated by Parodi et al., propranolol neither aggravated ischemia nor provided any protective effect; this is consistent with previous clinical reports.[8–11]

Although not seen in the 2 clinical trials cited in this report, beta-blockade can produce detrimental effects in patients with vasospastic angina. Yasue et al.[39] observed worsening of angina with propranolol in 13 patients with chest pain associated with S-T segment elevation. Robertson et al.[40] found that propranolol significantly prolonged the duration of ischemia as assessed by electrocardiographic monitoring in some patients with vasospastic angina; most of their patients, however, failed to notice any worsening or improvement of angina while taking propranolol despite the use of up to 640 mg daily of the drug. On the other hand, the finding of occasional responders to propranolol therapy (as documented in a single case in the study by Parodi et al.) suggests that this treatment may work in some individuals. This underscores the concept that mechanisms responsible for primary angina and vasospasm are multiple and remain largely unknown.

Although many investigators have reported beneficial results with the combination of verapamil and propranolol in angina of effort,[41,42] we do not recommend this combination in the treatment of angina at rest. Over the last decade, we have observed severe side effects caused by combination therapy consisting of bradycardia, transient asystole, severe hypotension, atrioventricular block, and congestive heart failure. Since the advantages of combination therapy in the management of rest angina lacks sound theoretical support, the frequency of adverse reactions has led us to avoid combination verapamil-propranolol treatment in patients with this syndrome.

Controlled *long-term* randomized trials comparing verapamil and propranolol in patients with angina at rest are yet to be performed. Thus, the controversy about the choice of the best medical long-term treatment in angina at rest has not been resolved.

Conclusions: Treatment with adequate dose of oral verapamil (360 to 480 mg daily) combined with long-acting nitrates appears to be the most effective and most rational therapy for patients with unstable vasospastic angina at rest. Although propranolol has been long considered the first-choice drug in most patients with angina pectoris, the drug does not appear useful in the management of most patients with this syndrome. The eventual place of propranolol in the management of unstable angina needs to be clarified and awaits a better understanding of the pathophysiology of ischemic heart disease.

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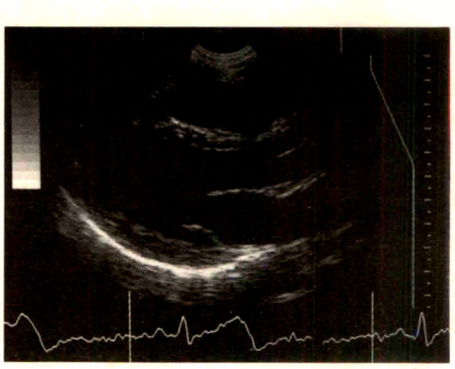

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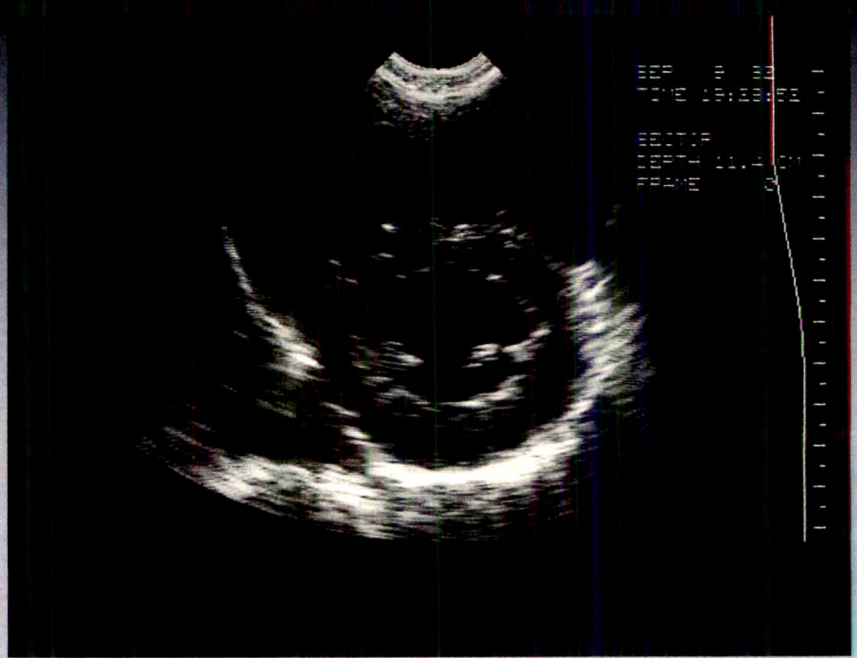

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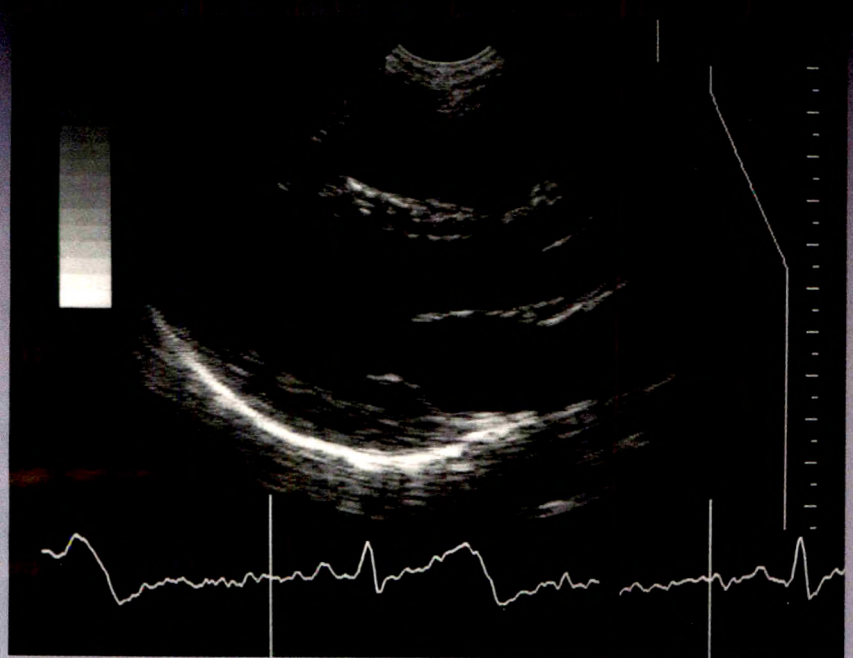

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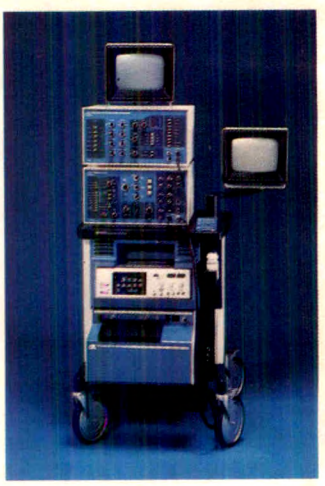

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LETTERS*

WITHDRAWAL OF 2 PREVIOUSLY PUBLISHED REPORTS

During 1981 I became aware of irregularities in data collected in my laboratory, as described in Section II of the Report of an Ad Hoc Advisory Committee to the Dean of the Harvard Medical School (*Harvard University Gazette*, January 29, 1982, Volume 77, page 1; and *Nature*, December 24, 1981, Volume 294, page 684).

This problem and further investigation have brought into question the validity of the data in the 2 reports listed below:

1. **Darsee JR, Kloner RA.** Dependency of location of salvageable myocardium on type of intervention. Am J Cardiol 1981;48:702–710.
2. **Darsee JR, Kloner RA.** The no reflow phenomenon: a time-limiting factor for reperfusion after coronary occlusion? Am J Cardiol 1980;46:800–806.

Because of the circumstances referred to above, it is my opinion that these reports should be retracted.

However, additional experiments have been carried out in my laboratory to examine the validity of the conclusions in these reports. These have validated the conclusions in the first report that drugs may result in both a lateral and subepicardial zone of salvage. These findings have been published. The observation that reperfusion results mainly in subepicardial salvage and the major concept in the second report that zones of microvascular damage occur within zones of myocardial cells which are already irreversibly damaged has also been confirmed, and the results have been submitted for publication.

Robert A. Kloner, MD, PhD, Department of Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts 02115

PROPER IDENTIFICATION OF TRADEMARKED PRODUCTS

I call your attention to an article in your March issue (Fuchs RM, Heuser RR, Yin FCP, Brinker JA. Limitations of pulmonary wedge V waves in diagnosing mitral regurgitation. Am J Cardiol 1982;49:849–854), in which the term "Swan-Ganz catheterization" is used to refer to a catheterization presumably performed using a flow-directed thermodilution catheter. Swan-Ganz is a registered trademark of American Hospital Supply Corporation, U.S. Trademark Registration No. 929,651. The term "Swan-Ganz" is registered for use with catheters. To use it, as the article does, to describe a surgical procedure is a misuse which, if repeated continually, would weaken and diminish our exclusive rights to use the Swan-Ganz trademark to identify our products.

We recognize that the article in question was submitted to you in approximately its present form and that the authors of the article and not your editors chose the term. It is nevertheless our hope that, by acquainting you with our concerns, we can enlist your cooperation for the future in using our Swan-Ganz trademark properly.

Enclosed is a brochure on proper trademark usage distributed by the United States Trademark Association. It is not our intent to presume to instruct the *Journal* and its editors on proper trademark usage, but instead to lend some authenticity to the need for proper use of our trademark by members of the public such as yourselves. Rule 6 in the brochure refers to the need and desirability of using a trademark to refer to the finished product and not to some other material or procedure. Thus, "Swan-Ganz catheter" or "Swan-Ganz thermodilution catheter" is a correct usage; "Swan-Ganz catheterization" or "Swan-Ganz balloon" is not. Your cooperation in using our Swan-Ganz mark in the recommended manner will be appreciated.

Robert E. Hartenberger, Trademark Counsel, American Hospital Supply Corporation, One American Plaza, Evanston, Illinois 60201

THE MORPHOLOGIC METHOD APPLIED TO THE PROBLEM OF "SINGLE" RIGHT VENTRICLE

Although Shinebourne et al.[1] claim to present 18 cases of single right ventricle ("univentricular heart of right ventricular type"), in fact they presented none. In addition to a large morphologically right ventricle, all of their cases also had a small morphologically left ventricle (LV). In single right ventricle, the left ventricle is absent (by definition), not just small.[2,3] Although the authors[1] presented no case of single right ventricle, which is a rare malformation,[2,3] they did make a good presentation of double inlet right ventricle, common inlet right ventricle, and mitral atresia in biventricular hearts with a large right ventricle and a small left ventricle.

The basic problem with the paper by Shinebourne et al.[1] is that these authors essentially accepted *the classic definition of single ventricle*[2,3]—that single ventricle is present when both atrioventricular (A-V) valves or a common A-V valve opens entirely or predominantly into 1 ventricular chamber. Unfortunately, this old definition leaves much to be desired. Briefly:

1. It is *wrong in principle* because it embodies an error in logic. This old definition attempts to define 1 variable (the anatomic status of the ventricles) primarily in terms of another variable (the anatomic status of the A-V valves). Instead, each variable should be defined primarily in terms of its own characteristics. For example, the anatomic status of the ventricles should be defined in terms of the morphologic characteristics of the ventricular portion of the heart, not in terms of any other variable, such as the A-V valves or the semilunar valves.

2. This old definition *violates the morphologic method* of diagnosing and naming the cardiac chambers in congenital heart disease. This method, which was introduced by Lev[4] in 1954 and has subsequently proved essential to the understanding of complex congenital heart disease,[2,3,5] may be stated as follows: (A) Cardiac chambers are diagnosed and named by means of their gross myocardial morphologic characteristics. (B) Cardiac chambers are not diagnosed and named by means of their vessels or *valves* of entry or exit, nor in terms of relative positions (such as right- or left-sided), nor in terms of the type or types of blood conveyed (such as arterial or venous), because all of these considerations are variables in congenital heart disease.

* Letters concerning a particular article in the *Journal* must be received within 2 months of the article's publication.

It is noteworthy that diagnosing and naming the anatomic status of the ventricles by means of the entering A-V valve or valves is specifically prohibited by the morphologic method. Unfortunately, this is precisely what the old definition of single ventricle attempts to do.

3. Because the classic definition of single ventricle is wrong in principle and is an unwitting violation of the morphologic method, it is not surprising that it has *numerous exceptions*. (A) Double inlet right ventricle and common inlet right ventricle may or may not have single right ventricle. Usually such hearts do *not* have a single right ventricle, accurately speaking; in terms of morphologic anatomic analysis, a small left ventricle usually also coexists. This is by far the most common exception to the classic definition of single ventricle. Ironically, this is the exception that was well explored by Shinebourne et al.[1] and was previously considered by Soto et al.[6] (B) With a single left ventricle, the straddling tricuspid valve can open predominantly into the infundibular outlet chamber, instead of predominantly into the single left ventricle as required by the classic definition. This anomaly is known as the *Lambert heart*.[7] (C) With a single left ventricle the tricuspid valve can open *exclusively* into the infundibular outlet chamber,[8] instead of predominantly into the single left ventricle as is required by the old definition.

Since the old definition of single ventricle is clearly unsatisfactory (being wrong in principle and a violation of the morphologic method and having at least 3 different types of exceptions), it should not be used as a model (paradigm) for the redefinition of single ventricle, nor for the redefinition of similar conditions such as straddling A-V valves and atretic A-V valves, nor for the redefinition of what is a *ventricle*, as opposed to what is merely a *rudimentary chamber*, as Shinebourne and his colleagues[1,9,10] have attempted to do.

For example, Shinebourne and his associates[1,9,10] have stated that when a straddling mitral valve opens 51 percent into the left ventricle and 49 percent into the right ventricle, then the left ventricle is called "the left ventricle" and the right ventricle is called "the right ventricle." However, when the straddling mitral valve opens only 49 percent into the left ventricle and 51 percent into the right ventricle, then the left ventricle must not be called "a left ventricle," but "a rudimentary chamber of left ventricle type," and the right ventricle must not be called "a right ventricle," but "the main chamber of a univentricular heart of right ventricle type."

There is much that is wrong with this approach.[1,9,10] First, the real reason for this assertion is failure to appreciate the deficiencies of the classic definition of single ventricle, on which this distinction between a ventricle and a rudimentary chamber is based. By essentially accepting the classic definition of single ventricle and attempting to build on it, Shinebourne and his colleagues[1,9,10] have unfortunately built on sand.

In view of its aforementioned deficiencies, the old definition of single ventricle must be supplemented by morphologic anatomic analysis[2,3] in order to ensure anatomic accuracy. Whenever conclusions based on morphologic analysis come into conflict with interpretations based on an old definition (such as that of single ventricle), the results of morphologic analysis should be preferred—particularly when the old definition is flawed, as in the case of the old definition of single ventricle.

To say that a left ventricle is not a left ventricle unless it receives 50 percent or more of the mitral valve is analogous to saying that the morphologically left atrium is not the left atrium unless it receives at least 2 of the 4 pulmonary veins. However, in totally anomalous pulmonary venous connection, the left atrium is still the left atrium, even though it receives no pulmonary veins. In total anomalous pulmonary venous connection, although the left atrium is not normal, it is a left atrium nonetheless. To call the left atrium "an accessory chamber" would serve no useful purpose and would merely be another violation of the morphologic method and of the aforementioned principle of logic.

Taxonomically, this approach[1,9,10] is not practical. For example, it is not helpful for the names of the ventricular chambers to change depending on the degree of straddling of the A-V valves.

Anatomically, this approach[1,9,10] is not realistic. A straddling mitral valve is not 51 percent above the left ventricle and 49 percent above the right ventricle, or vice versa. In both hypothetical situations, the straddling mitral valve is mainly above the ventricular septum. The foregoing is conceptual anatomy, not realistic anatomy.

Diagnostically, this approach[1,9,10] is not practical. Angiocardiographically, echocardiographically, and even surgically, one cannot distinguish 51 percent straddling of the mitral valve or tricuspid valve from 49 percent straddling.

Surgically, this approach[1,9,10] is not helpful. For example, just because the straddling tricuspid valve opens more into the left ventricle than into the right ventricle, it does not necessarily follow that a single left ventricle is therefore present. In this situation, a good-sized right ventricle can coexist and this anatomic fact can be of considerable surgical importance. Anatomic inaccuracy is not helpful surgically.

To summarize, the morphologic method described should be used to diagnose and to name the cardiac chambers. In single right ventricle, accurately speaking, the left ventricle is absent (not just small). A valid distinction exists between double inlet right ventricle and common inlet right ventricle with a biventricular heart (large right ventricle and small left ventricle) on the one hand, and double inlet right ventricle and common inlet right ventricle with single right ventricle (large right ventricle and absent left ventricle) on the other. Shinebourne et al.[1] presented double inlet right ventricle, common inlet right ventricle, and mitral atresia in biventricular hearts with a large right ventricle and a small left ventricle. The classic definition of single ventricle is not satisfactory for 3 main reasons: (1) it is wrong in principle; (2) it violates the morphologic method; and (3) it has numerous well-documented exceptions. Consequently, this unsatisfactory old definition should not be used as a model (paradigm) for deciding what is a ventricle versus what is merely a "rudimentary chamber." Naming ventricular chambers in terms of the degree of straddling of the A-V valves is wrong in theory and also leaves much to be desired in practice: As exemplified previously, this approach is anatomically inaccurate, diagnostically impractical, and surgically unhelpful. No one can take refuge in a definition when that definition is unacceptable. Nor should anyone wish to. There is no good reason to insist on applying the classic concept of single ventricle when modern morphologic anatomic analysis and the principles of logic both indicate that this old concept is untenable. Instead, we should all adhere to the morphologic method of diagnosing and naming the cardiac chambers in complex congenital heart disease[2–5,11] because this approach is acceptable both in theory and in practice. Many scientific controversies are not really disagreements at all, but rather are the results of misunderstanding. This is the root problem here. Precisely what is wrong with the classic definition of single ventricle has not been clearly understood until recently. Hence, it has not been widely appreciated that attemptes to apply this old approach in an effort to redefine what a ventricle is (and is not) are similarly unacceptable. Together, all serious students of congenital heart disease must choose an approach that is, and

will continue to be, satisfactory for the field as a whole. The approach must be sound. We must not choose, or defend, an approach that we all should now know is wrong in theory, and unsatisfactory in practice.

Richard Van Praagh, MD, Ronald D. Leidenfrost, MD, Sung Kyu Lee, MD, Gerald Marx, MD, Gregory B. Wright, MD, and Stella Van Praagh, MD, Departments of Pathology and Cardiology, Children's Hospital Medical Center and, Harvard Medical School, Boston, Massachusetts

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REPLY

We have carefully analyzed the letter of Van Praagh and his colleagues, as, indeed, we analyzed with similar care their earlier letter[1] concerning the work of Soto et al. on the anomaly under discussion. In descriptive terms, the malformations described had their atrial chambers connected only to a morphologically right ventricular chamber in presence of a second left ventricular chamber which lacked an atrioventricular connection. It seems that Van Praagh et al. object to this anomaly being considered as "single right ventricle." We sympathize with them in this respect, which is why we specifically chose *not* to call the hearts "single right ventricle." Reading their letters we infer that the major concern of Van Praagh et al. is to preserve the purity of their own definitions of single ventricle. It is precisely because we respect this prerogative that we chose the term "univentricular" rather than "single ventricle" when looking for a word that would group together several congenital malformations which, among themselves, differed in other aspects of morphology. We believe that the concept that justifies this grouping is entirely logical, is internally consistent, and is based completely on observed morphology. It would be possible to rebut each of the criticisms of Van Praagh's group in turn, but it is perhaps better to try to summarize the basis of our own method for categorization of hearts in general,[4] but particularly the hearts we choose to group as univentricular.[5–8]

The system we advocate is based on analysis of the junctions of the heart in terms of type and mode of connection, analysis of the chambers and great arteries in terms of both observed morphology and their size and analysis of the interrelations of chambers and arteries. All features are described when necessary, but with mutually exclusive terms. Considering this in the light of our use of "univentricular," congenital malformations as a whole can be divided into 2 groups on the basis of their atrioventricular (A-V) connections. In by far the largest group, there is a one to one connection between the atria and the ventricles. In the second group, only one ventricular chamber is connected to the atria. A second ventricular chamber, if present in this group, lacks an A-V connection. The chamber that lacks an A-V connection can vary markedly in size (which we describe) without this affecting its basic morphology. To argue that this difference in connection or nonconnection of a ventricular chamber to the atria does not alter its own intrinsic morphology—which we understand is what Van Praagh et al. suggest—is reducing the situation to the absurd. It suggests that Occam's razor, when wielded without care, has the effect of a guillotine.

In the group with one to one A-V connections, each ventricular chamber is connected via a parietal A-V junction to an atrial chamber. This fact can be recognized simply by examining the structure of each ventricular chamber. Equally, in the other group with only one ventricular chamber connected to the atria, this structure can again be determined solely by examining the ventricular chambers. The basic feature that unifies the hearts we have chosen to term "univentricular" is therefore that they posses only 1 ventricular chamber that is connected to the atrial chambers. Whether or not this is based on old flawed definitions is neither here nor there. The grouping together of these hearts recognizes a feature of major diagnostic, clinical, and surgical significance that warrants attention from all those interested in congenital heart disease. The hearts that are justifiably unified by this morphologic feature can, of course, differ in respect to the detailed morphology of their ventricular mass. This also demands description in unambiguous fashion. From our observations and those of many others, we conclude that hearts with the A-V junction connected to only one ventricular chamber can have three basic patterns of morphology. The most common is when the chamber connected to the atria has left ventricular morphology and the chamber lacking an A-V connection has right ventricular morphology. Although Van Praagh et al. claim that this second chamber is solely an infundibulum, our observations[4–8] militate against this possibility. Indeed, our findings suggest unequivocally that it possesses a trabecular component of right ventricular type. This trabecular component can exist in isolation when both outlets are connected to the left ventricular chamber.[7] Our further observations show that a second variety of hearts exists with the atria connected to only 1 ventricular chamber. This second variety is entirely analogous to the first variety. The first variety is described by Van Praagh and colleagues as "single left ventricle." The second variety is characterized by the chamber connected to the atria having right ventricular characteristics and that not connected to the atria having left ventricular characteristics.[3,8,9] Our observations show that this unequivocally left ventricular chamber, recognizable from its own morphology as lacking an A-V connection, can also exist in isolation as a trabecular component when both outlets are connected to the right ventricular chamber, or can have its own outlet portion.[8,9] Our observations go further still in that they indicate that a third comparable variety of hearts exist in which the A-V connection is committed to a sole chamber in the ventricular mass.[8] This sole chamber is characterized by neither right nor left ventricular trabecular patterns but has an indeterminant pattern. The final vital point we have found is that any of these 3 ventricular morphologies—left

ventricular main chamber with right ventricular rudimentary chamber, right ventricular main chamber with left ventricular rudimentary chamber, or sole chamber of indeterminate morphology—can exist when the A-V connection is double inlet or when either the right or left A-V connection is absent.[8] When a rudimentary chamber is present, the A-V connection cannot be determined simply by examining the rudimentary chamber, since its morphology of either right or left ventricular type is virtually identical be there double inlet or absent connection.[6,8]

Van Praagh and his colleagues are perhaps most concerned with our treatment of hearts with straddling and overriding valves. It is generally accepted that such hearts make up a series of anomalies between hearts with one-to-one atrioventricular connections and those with the atria connected to only 1 ventricular chamber. There are 2 ways of dealing with such a series. The first is to consider such hearts as a discrete type of connection. The second is to consider an overriding valve as a mode of connection, and to divide the series of which it is a part at its mid-point, categorizing only the 2 ends of the series in terms of atrioventricular connections. It is the latter approach which we adopt. But then the decision regarding categorization is not arbitrary, it is determined by the observed structure of the overriding valve and its precise connections to the underlying ventricular chambers.

The vital point, therefore, which Van Praagh and his colleagues apparently misunderstand, is that although we are concerned with the effect that inlets and outlets have on ventricular morphology, and are equally concerned about chamber size, we do *not* define ventricular morphology solely in terms of a valve of entry. We try to describe all features of ventricular morphology, both their architecture and their size. A ventricular chamber of any type is given specificity by its trabecular component, be it that of left ventricular, right ventricular, or indeterminate type. Indeed, the term "ventricle" itself is as nonspecific as is "outlet chamber" or "trabecular pouch" when unequalified as to the nature of its trabecular component. Simply from observed morphology it is evident that right and left ventricular chambers can exist together, both having inlet and outlet components as in the normal heart. Right and left ventricular chambers can also exist together when 1 has an inlet alone and the other has an inlet and both outlets as in double outlet ventricles. These structures are found only in hearts with one to one A-V connections. But equally left and right ventricular chambers can exist together when 1 ventricular chamber lacks an inlet component. The atrial chambers are then either both connected to the other ventricular chamber, or else one atrium has no A-V connection. In this setting, the very finding of a ventricular chamber *without* an A-V connection, which we choose to call a rudimentary chamber, announces almost without exception that the A-V junction is connected to only 1 ventricular chamber. But this finding also makes it necessary to give specificity both to the chamber connected to the atria (which we call a ventricle) and to the chamber lacking an A-V connection (the rudimentary ventricular chamber). This must be done not only by describing their being of right or left ventricular type but also by describing their size. It also makes it necessary to determine the precise A-V connection present. Indeed, the recognition that a heart belongs to the group we term "univentricular" sets in motion a train of events that leads inexorably to the correct clinical diagnosis.

What is questionable is whether we are justified in using the term "univentricular" for grouping together these hearts. We have in fact commented on the literary inadequacy of using the term "univentricular" for describing hearts possessing 2 ventricular chambers.[7] We stated clearly at that time that the only justification for using "univentricular" in this fashion was the continuing use of "single ventricle" to describe hearts possessing 2 ventricular chambers. Van Praagh et al. are therefore incorrect when they imply that we are unacquainted with the deficiencies of the classic definition of "single ventricle." But it is evident even from this recent letter that the classic convention is still very much alive, and that he and his colleagues still describe as "single ventricle" hearts that possess 2 chambers within their ventricular mass. Investigators must use the terminology most suited to their needs. In the case of hearts in which the A-V junction is connected to only 1 ventricular chamber, and in the differentiation of these hearts from each other and from other hearts with imperforate A-V valves, we find our own described nosology[8–10] most adequate. We see no reason to change this nosology, which is of immense value in clinical situations, simply because it contravenes the purity of definition of an anomaly that other authorities would term "single right ventricle." Our own system caters for all examples known to us of what might be termed "single ventricle" and also groups with them many analogous hearts. We find no new evidence within the comments of Van Praagh and his colleagues that warrants change in their approach.

Elliot A. Shinebourne, MD, Giuseppe Calcaterra, MD, Kai-Chiu Lau, MD, and Robert H. Anderson, MD

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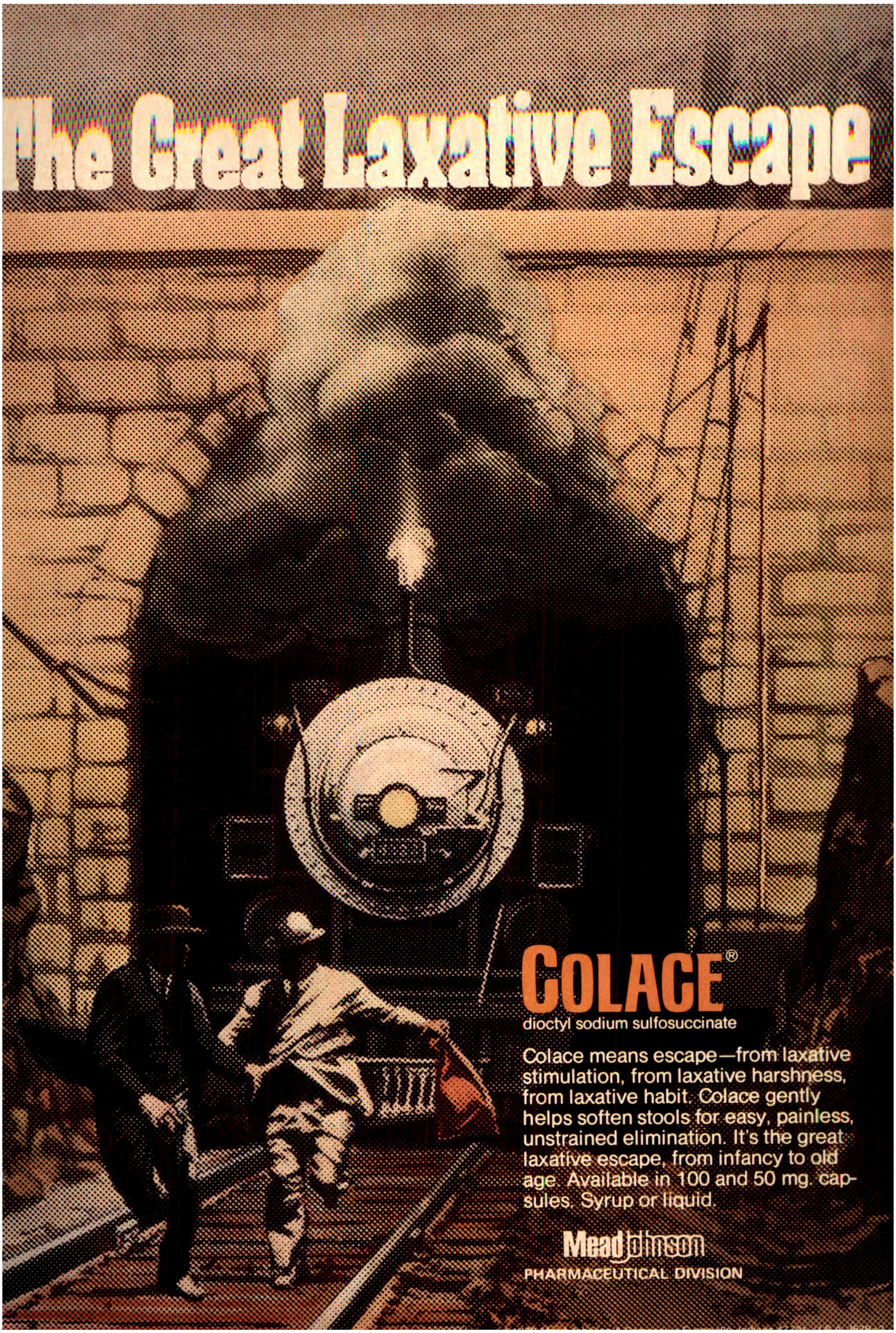
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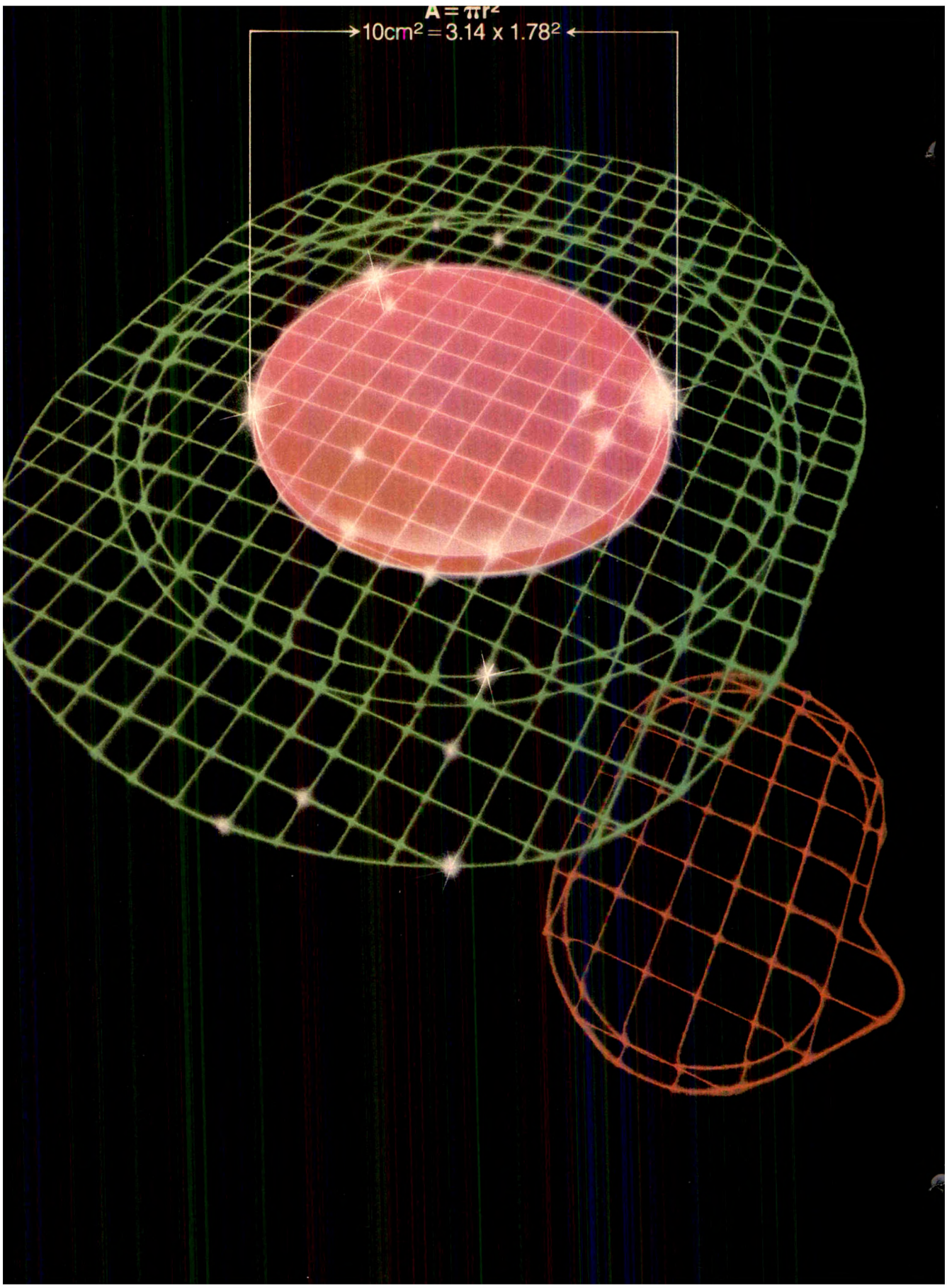
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References: 1. Michaels AS, Chandrasekaran SK, Shaw JE: *AIChE Journal 21*(5):993, September 1975. **2.** Data on file, Key Pharmaceuticals, Inc.

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DESCRIPTION: The Nitro-Dur Transdermal Infusion System contains nitroglycerin in a gel-like matrix composed of glycerin, water (purified), lactose, polyvinyl alcohol, povidone and sodium citrate to provide a continuous source of the active ingredient. Nitro-Dur is available in dosage sizes 10cm², 15cm² and 20cm², containing 51 mg, 77 mg and 104 mg of nitroglycerin, respectively, thereby providing precise dosing levels of nitroglycerin. Nitro-Dur has a rated release *in vivo* of approximately 0.5mg/cm²/24 hours. Each unit is sealed in a polyester-foil-polyethylene laminate. The bandage portion consists of a medical grade non-woven, heat sealable, microporous tape.

CLINICAL PHARMACOLOGY: When the Nitro-Dur system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In bioavailability studies,[1] transdermal absorption of nitroglycerin from the gel-like matrix achieved steady state venous plasma levels comparable to that of sublingual nitroglycerin and maintained these levels for 24 hours. Therapeutic effect is achieved within 30 minutes after application of the unit, and persists about 30 minutes after removal of the unit.

INDICATIONS AND USAGE: Prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS: The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the Nitro-Dur dosage should be reduced or use of the product discontinued.

HOW SUPPLIED: Nitro-Dur Transdermal Infusion System, 10cm², 15cm² and 20cm², is available in unit dose packages of 28.

CAUTION: Federal law prohibits dispensing without a prescription.

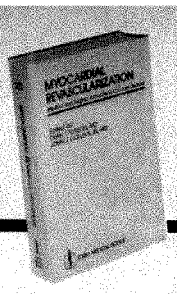
PATIENT INSTRUCTIONS FOR APPLICATION: Patient instructions are furnished with each unit dose package.

For complete prescribing information, please see package insert.

[1]Data on file: Key Pharmaceuticals, Inc. 0882

KEY PHARMACEUTICALS, INC.
Miami, Florida 33169

World leader in drug delivery systems.



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CARDIOLOGY: 1982

The Second Issue of the New Annual providing a multidisciplinary approach to the latest, most important information on the state-of-the-art of cardiovascular medicine and surgery

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- **Dean T. Mason, M.D.**
  Professor of Medicine and Physiology, and Chief of Cardiovascular Medicine, University of California, Davis School of Medicine and University Medical Center, Davis and Sacramento, California
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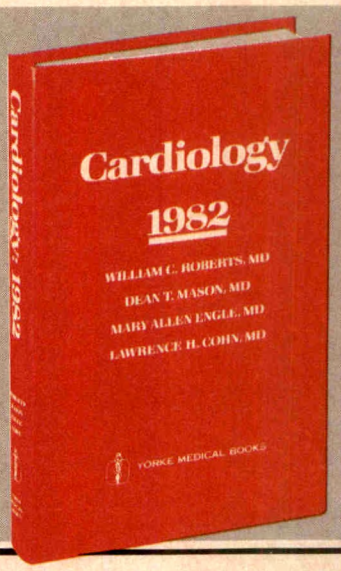

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- A multidisciplinary approach to clinical and applied research based on an exhaustive search of the year's literature
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CARDIOLOGY:1982 is NOT

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- An abstracting service
- A rehash of materials readily available elsewhere

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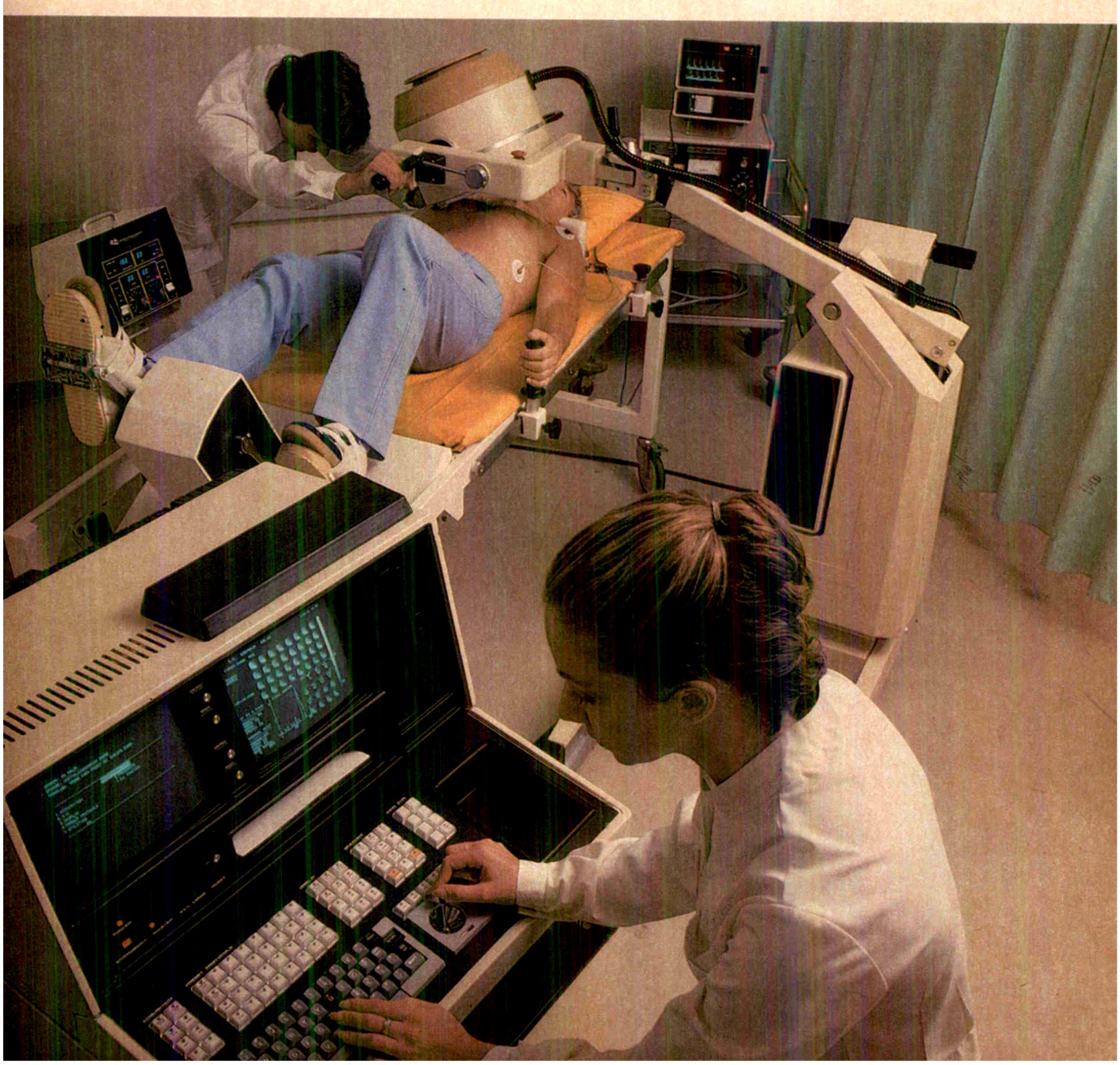

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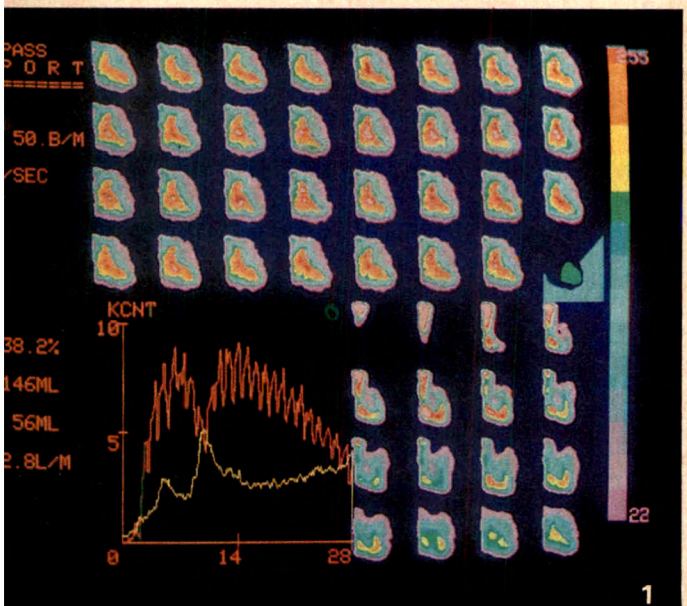

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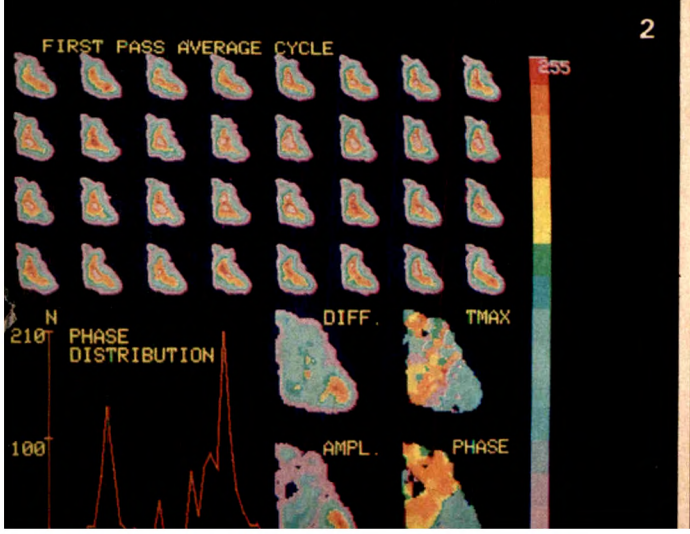

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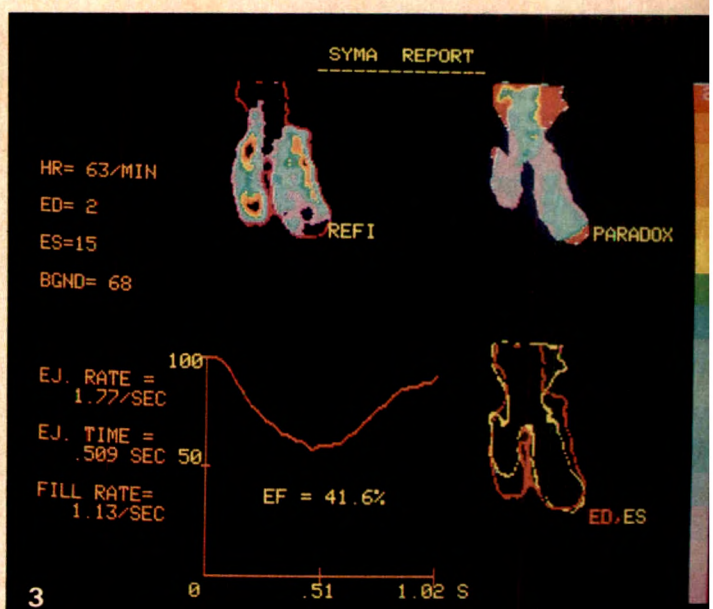
Photos 1 & 2: Apex 215M's high count rates enable superior definitive first-pass studies. Typical of its capabilities are global and regional ventricular function analysis and direct quantification through volume.



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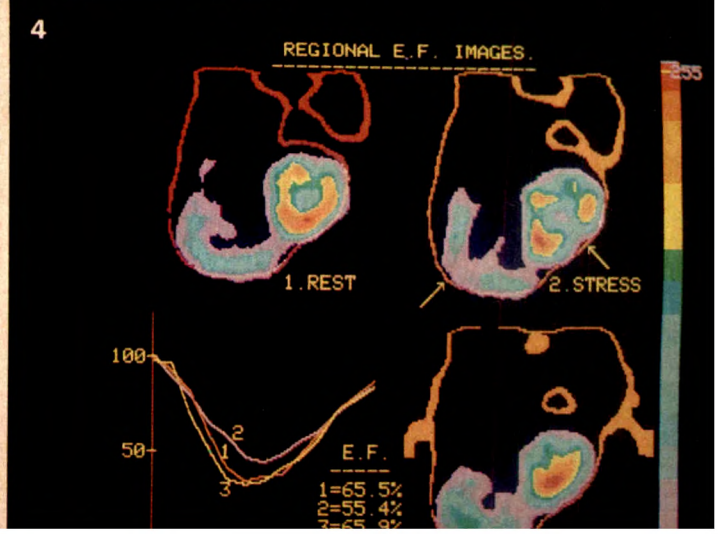

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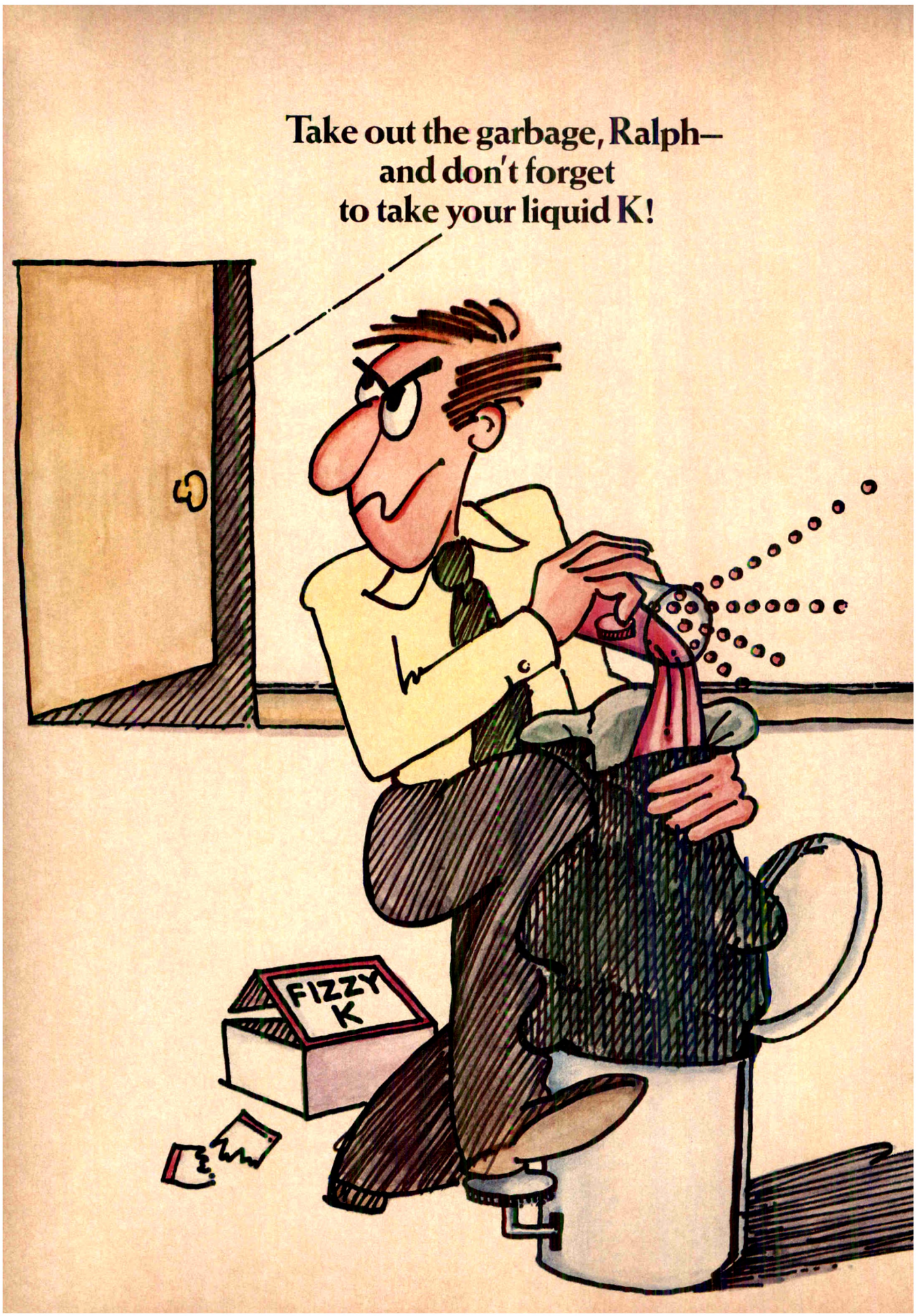
Photos 3 & 4: Apex 215M can clearly display various global and regional functions on a single image monitor. In these examples, ventricular functions in a resting heart appear above; the lower image compares the resting heart with two different intervention situations.


Take out the garbage, Ralph–
and don't forget
to take your liquid K!
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CIBA 185

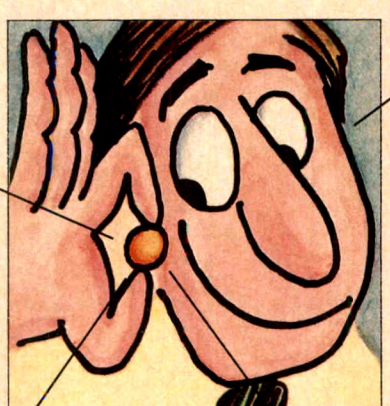
potassium chloride slow-release tablets 8 mEq

In correcting diuretic-induced alkalosis

the tablet that offers therapeutic substance...not fizz

Nonchloride tablets and liquids fizzle out in correcting hypochloremic alkalosis

Citrate/bicarbonate or gluconate effervescent tablets and liquids such as K-Lyte® and Kaon® elixir lack the essential chloride to correct diuretic-induced hypochloremic alkalosis.



Slow-K—first in physician and patient acceptance

"This compound [Slow-K] is effective, convenient, well tolerated...and also appears to have greater patient acceptability than comparable doses of liquid potassium chloride compounds."[1]

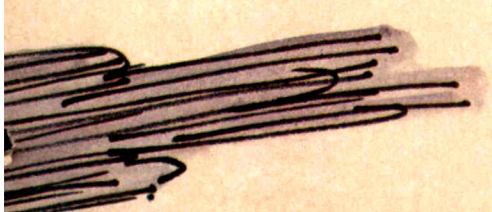
Unrivaled clinical experience

No other tablet can claim over 7 years' U.S. clinical experience in over 5 million patients.*

Easy on the budget

A day's therapy averages only 25¢.†

Slow-release potassium chloride preparations should be reserved for patients who cannot tolerate, refuse to take or have compliance problems with liquid or effervescent potassium preparations, because of reports of intestinal and gastric ulceration and bleeding with slow-release KCl preparations.



*Data on file, CIBA Pharmaceutical Company.

†Average cost per day based on Pharmaceutical Data Services audit.

Please see next page for brief Prescribing Information.

CIBA

Reference: 1. Gunnells JC, Orgain ES, McGuffin WL, Jr. Treatment of systemic hypertension. In *The Heart* (ed. 4). Hurst JW, Logue RB, Schlant RC, Wenger NK (Eds.). New York, McGraw-Hill Book Company, 1978. p 1439.

SLOW-K® potassium chloride slow-release tablets

DESCRIPTION

Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS

BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS

In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS

Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS

Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion, particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram, and clinical status of patient.

ADVERSE REACTIONS

Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION

Usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

C81-72 (1/25/82)

128-3476-A

Consult complete product literature before prescribing.

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation

CIBA

Xylocaine®
(lidocaine HCl) Solution
Intravenous Injection for Ventricular Arrhythmias

Before prescribing or administering, please consult complete product information, a summary of which follows:

INDICATIONS

Xylocaine brand of lidocaine HCl administered intravenously is specifically indicated in the acute management of (1) ventricular arrhythmias occurring during cardiac manipulation such as cardiac surgery, and (2) life-threatening arrhythmias which are ventricular in origin, such as occur during acute myocardial infarction.

CONTRAINDICATIONS

Xylocaine brand of lidocaine HCl is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type. Xylocaine brand of lidocaine HCl should not be used in patients with STOKES-ADAMS syndrome, Wolff-Parkinson-White syndrome, or with severe degrees of sinoatrial, atrioventricular, or intraventricular block.

WARNINGS

Constant monitoring with an electrocardiograph is essential to the proper administration of Xylocaine brand of lidocaine HCl intravenously. Signs of excessive depression of cardiac conductivity, such as prolongation of PR interval and QRS complex and the appearance or aggravation of arrhythmias, should be followed by prompt cessation of the intravenous infusion of this agent. It is mandatory to have emergency resuscitative equipment and drugs immediately available to manage possible adverse reactions involving cardiovascular, respiratory, or central nervous systems.

Occasional acceleration of ventricular rate may occur when Xylocaine brand of lidocaine HCl is administered to patients with atrial fibrillation. Evidence for proper usage in children is limited.

Usage in Pregnancy: It is not known whether Xylocaine brand of lidocaine HCl may have adverse effects upon fetal development. The benefits of the drug to the mother should be weighed against the possible risk to the fetus.

PRECAUTIONS

Caution should be employed in the repeated use of Xylocaine brand of lidocaine HCl in patients with severe liver or kidney disease because accumulation may occur and lead to toxic phenomena, since Xylocaine brand of lidocaine HCl is metabolized mainly in the liver and excreted by the kidneys. The drug should also be used with caution in patients with hypovolemia and shock, and in all forms of heart block (see CONTRAINDICATIONS and WARNINGS).

In patients with sinus bradycardia or incomplete heart block, the administration of Xylocaine brand of lidocaine HCl intravenously or the elimination of ventricular ectopic beats without prior acceleration in heart rate (e.g., by isoproterenol or by electric pacing) may promote more frequent and serious ventricular arrhythmias or complete heart block (see CONTRAINDICATIONS).

ADVERSE REACTIONS

Systemic reactions of the following types have been reported:

1) Central Nervous System:
Light-headedness; drowsiness; dizziness; apprehension; euphoria; tinnitus; blurred vision or double vision; vomiting; sensations of heat, cold or numbness; twitching; tremors; convulsions; unconsciousness; respiratory depression and arrest.

2) Cardiovascular System:
Hypotension; cardiovascular collapse; and bradycardia which may lead to cardiac arrest.

3) Allergic reactions may occur but are infrequent. There have been no reports of cross-sensitivity between Xylocaine brand of lidocaine HCl and procainamide or between Xylocaine brand of lidocaine HCl and quinidine.

MANAGEMENT OF ADVERSE REACTIONS

1) In the case of severe reaction, discontinue the use of Xylocaine brand of lidocaine HCl.

2) Institute emergency resuscitative procedures and administer the emergency drugs necessary to manage the severe reaction. For severe convulsions, small increments of diazepam or an ultrashort acting barbiturate (thiopental or thiamylal); or if those are not available, a short-acting barbiturate (pentobarbital or secobarbital); or if the patient is under anesthesia, a short-acting muscle relaxant (succinylcholine) may be given intravenously. Muscle relaxants and intravenous medications should only be used by those familiar with their use. Patency of the airway and adequacy of ventilation must be assured.

3) Should circulatory depression occur, vasopressors, such as ephedrine, or metaraminol may be used.

HOW SUPPLIED

For direct injection Xylocaine brand of lidocaine HCl without preservatives is supplied in 5 ml, 100 mg ampules and in 5 ml, 100 mg prefilled syringes.

For preparing intravenous infusion solutions, Xylocaine brand of lidocaine HCl without sodium chloride or preservatives is supplied in one and two gram additive syringes and in one and two gram single use vials. Each vial is packed with a pre-sterilized transfer unit manufactured by the West Company.

ASTRA®

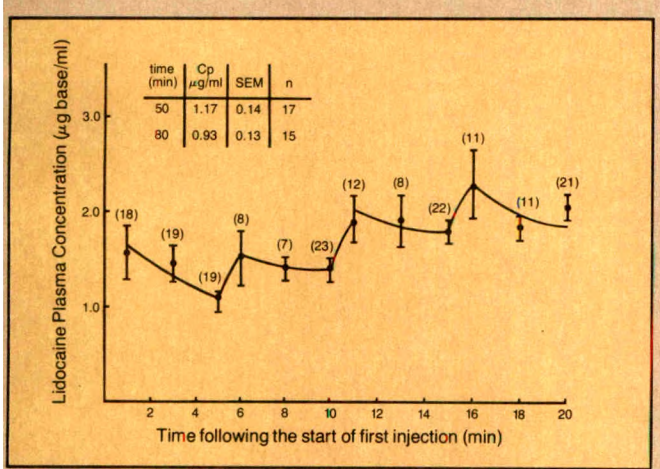
Astra Pharmaceutical Products, Inc.
Worcester, Massachusetts 01606

AST-2305

Advances in Cardiac Antiarrhythmic Techniques

INFARCT

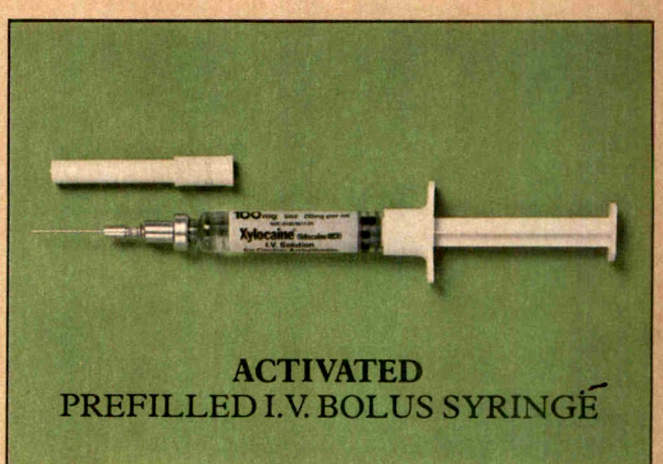
Multiple bolus injections of Xylocaine® (lidocaine HCl) Solution in the first 16 minutes of administration may control refractory ventricular extrasystoles.[1]



Plasma concentration-time data (mean ± standard error of the mean [SEM]) observed after administration of a total of 225 mg of lidocaine in divided bolus doses every 5 minutes over a 16-minute period. Cp = plasma concentration; n = number of plasma determinations at 50 and 80 minutes; figures in parentheses = number of plasma determinations at the times indicated.[1]

In patients with acute myocardial infarction, serious ventricular extrasystoles sometimes continue to occur even after an initial bolus dose of 75 mg lidocaine and concomitant 2 mg/min lidocaine infusion. Multiple bolus injections of 50 mg lidocaine — every 5 minutes if necessary to a total of 225 mg lidocaine — have been shown to be a safe way to provide effective, nontoxic blood levels of lidocaine in these patients.[1] In 23 patients given divided doses of 75, 50, 50, and 50 mg lidocaine by bolus injection at 5-minute intervals over a 16-minute period, no plasma concentration greater than 4.8 μg/ml was observed. Plasma concentrations stayed well within the accepted therapeutic range during virtually all of this period.[1]

When your protocol calls for multiple bolus injections of lidocaine, choose the Xylocaine® I.V. Bolus 100 mg Syringe.



ACTIVATED
PREFILLED I.V. BOLUS SYRINGE

The locked needle guard ensures sterility, and indicates the needle has not been exposed. The calibrated barrel has clear markings for 100 mg and 50 mg doses, simplifying administration. And the finger grips make it easy to administer slowly a controlled I.V. bolus injection. Remember that NO MORE THAN 200 TO 300 MG OF LIDOCAINE HCl SHOULD BE ADMINISTERED DURING A ONE-HOUR PERIOD.

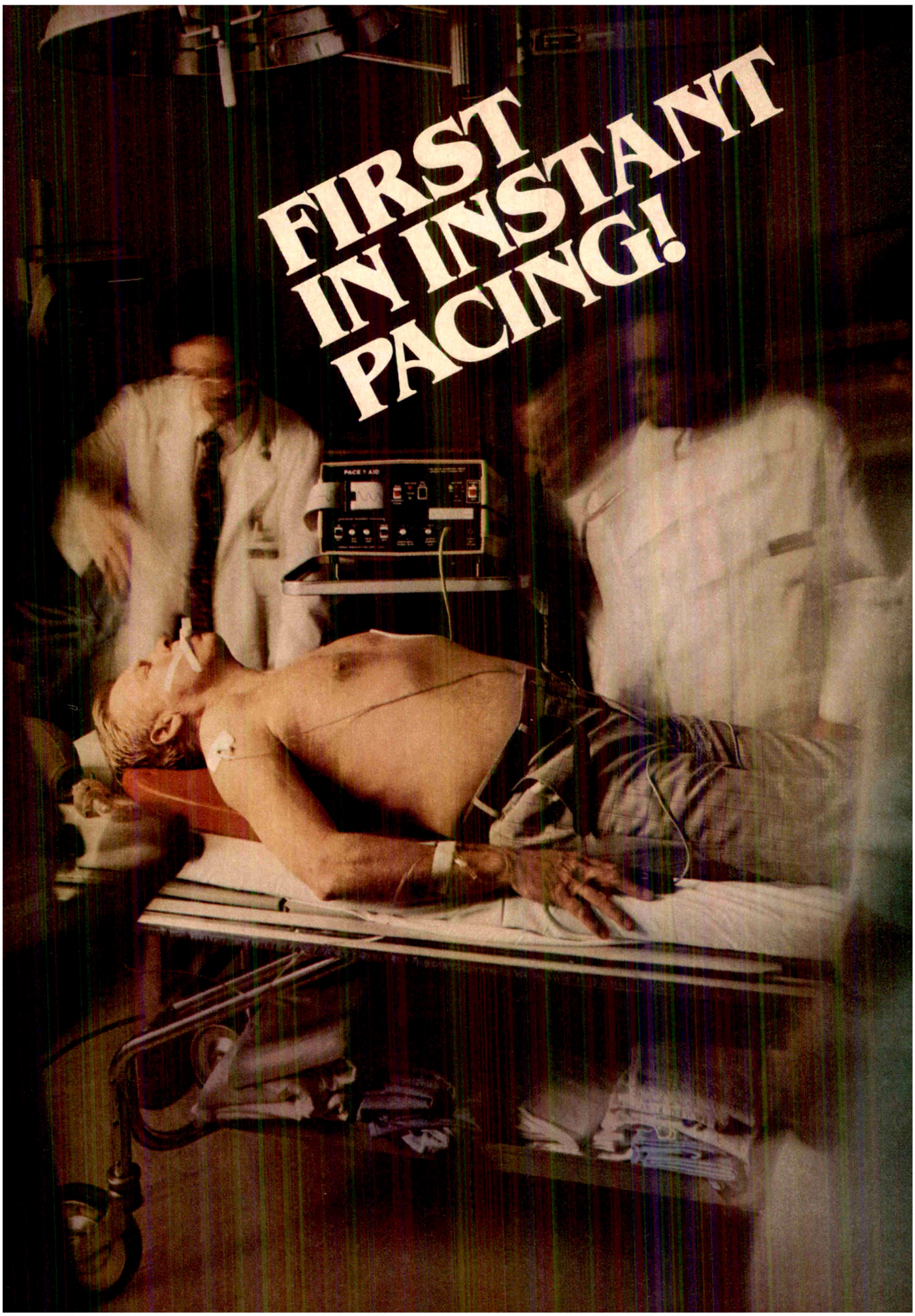
Xylocaine®
(lidocaine HCl) Solution

The most complete system for ventricular arrhythmias

ASTRA® | Astra Pharmaceutical Products, Inc.
Worcester, Massachusetts 01606

Please see next page for a summary of prescribing information.

REFERENCE: 1. Wyman, MG, et al: Multiple bolus technique for lidocaine administration during the first hours of an acute myocardial infarction. *Am J Cardiol* 41: 313-317, 1978.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IN INSTANT
PACING!

Announcing a unique, noninvasive emergency pacemaker

PACE AID™

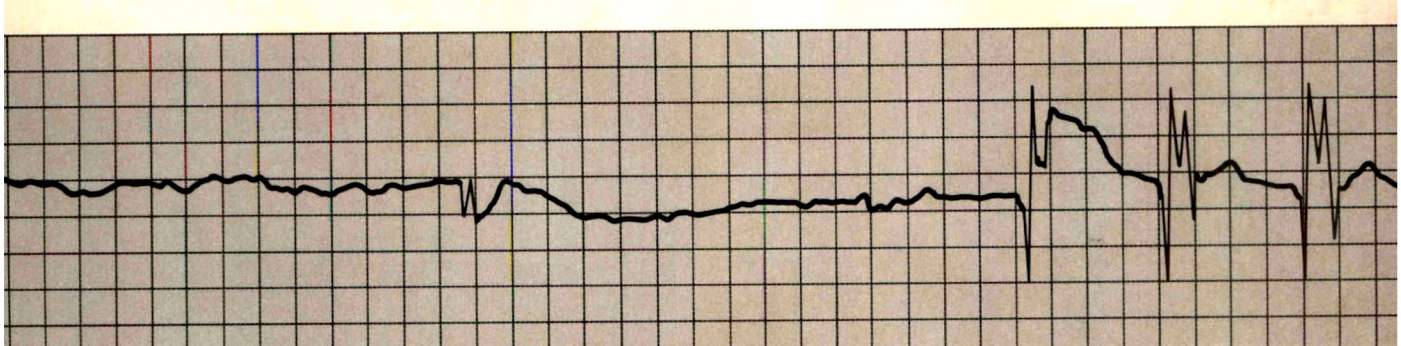
The major remaining problems in the management of cardiac arrest are asystole and severe bradycardia....

Now PACE AID provides immediate therapy

- ☐ easy application with anterior/posterior adhesive electrodes
- ☐ portable/battery powered
- ☐ buys time to start endocardial pacing
- ☐ for ED, ICU, CCU and mobile cardiac care units
- ☐ no defibrillator should be without one

Cardiac arrest patient with asystole and ventricular escape beat.

Noninvasive PACE AID pacing at 80/min – blood pressure 110/80 mm Hg.*



*Data on file, Cardiac Resuscitator Corporation.

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The Pacekeeper™

For steady maintenance following cardioversion of supraventricular, ventricular, and atrial tachyarrhythmias

- Maintains normal sinus rhythm
- Full quinidine cardiodynamics
- Greater gastrointestinal tolerance than with quinidine sulfate*
- Convenient b.i.d. or t.i.d. dosage

*Bibliography available upon request.

CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

INDICATIONS AND USAGE: CARDIOQUIN Tablets are indicated as maintenance therapy after spontaneous and electrical conversion of atrial tachycardia, flutter or fibrillation and in the treatment of premature atrial and ventricular contractions, paroxysmal atrial tachycardia, paroxysmal A-V junctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when therapy is appropriate, andparoxysmal ventricular tachycardia when not associated with complete heartblock. CONTRAINDICATIONS: History of hypersensitivity to quinidine, complete A-V block, complete bundle branch block or other severe intraventricular conduction defects, myasthenia gravis, arrhythmias associated with digitalis toxicity. WARNINGS: In the treatment of atrial fibrillation with rapid ventricular response, use digitalis to control ventricular rate prior to administration of quinidine. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine. *Potentially toxic digoxin plasma levels may occur when quinidine is administered concurrently. Consider reducing digoxin dosage and monitoring for digitalis toxicity.* Evidence of quinidine cardiotoxicity (increased P-R and Q-T intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia) mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. NOTE: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia. Quinidine should be used with extreme caution in the presence of incomplete A-V block, since complete block and asystole may result. Quinidine may cause abnormalities of rhythm in digitalized patients; therefore, it should be used with caution in the presence of digitalis intoxication. Caution is also called for in patients exhibiting renal, cardiac or hepatic insufficiency because of potential toxic accumulation of quinidine in plasma. PRECAUTIONS: A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncracy to quinidine. ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered. Periodic blood counts and liver and kidney function tests should be performed during long-term therapy.

DRUG INTERACTIONS OF QUINIDINE

DRUG	EFFECT
With anticholinergic drugs	Additive vagolytic effect.
With cholinergic drugs	Antagonism of cholinergic effects.
With carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreas excretion of quinidine.
With coumarin anticoagulants	Reduction of clotting factor concentrations
With tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade.
With phenothiazines and reserpine	Additive cardiac depressive effects.
With hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine.
With digoxin	Increased plasma concentrations of digox (see WARNINGS).

PREGNANCY: The use of quinidine in pregnancy should be reserved only for those cases whe the benefits outweigh the possible hazards to the patient and fetus. NURSING MOTHERS: Th drug should be used with caution due to excretion of the quinidine in breast milk. ADVERS REACTIONS: SYMPTOMS OF CINCHONISM (ringing in the ears, nausea, headaches, and/ disturbed vision) may appear in sensitive patients after a single dose of the drug. GASTROINTES TINAL: Diarrhea, nausea, vomiting, abdominal pain. CARDIOVASCULAR: Widening of QR complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms (including ventricul tachycardia and fibrillation), paradoxical tachycardia, arterial embolism, and hypotension. HEMA TOLOGIC: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranul cytosis. CNS: Headache, fever, vertigo, apprehension, excitement, confusion, delirium, an syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasi blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, nigh blindness, scotomata), optic neuritis. DERMATOLOGIC: Rash, cutaneous flushing with intens pruritus, urticaria. HYPERSENSITIVITY REACTIONS: Angioedema, acute asthmatic episod vascular collapse, respiratory arrest, hepatic toxicity. See package insert for Full Prescribin Information.

Purdue Frederick

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NOVEMBER 1982

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The American Journal of CARDIOLOGY®

Symposium on Verapamil Therapy for Angina Pectoris: Part III

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Contents on Page A9

When more than a thiazide is needed...

ALDOMET® TABLETS 500 mg, 250 mg, and 125 mg (METHYLDOPA | MSI

an agent well matched to the prc fil

With increasing age...
incidence of certain concurrent disorders increases

ALDOMET may be used in a wide range of older hypertensives, including those with:

- **ventricular hypertrophy/cardiac failure***
- **peripheral vascular disease**
- **diabetes mellitus**
- **hyperuricemia/gouty arthritis**

judicious exercise may be desirable

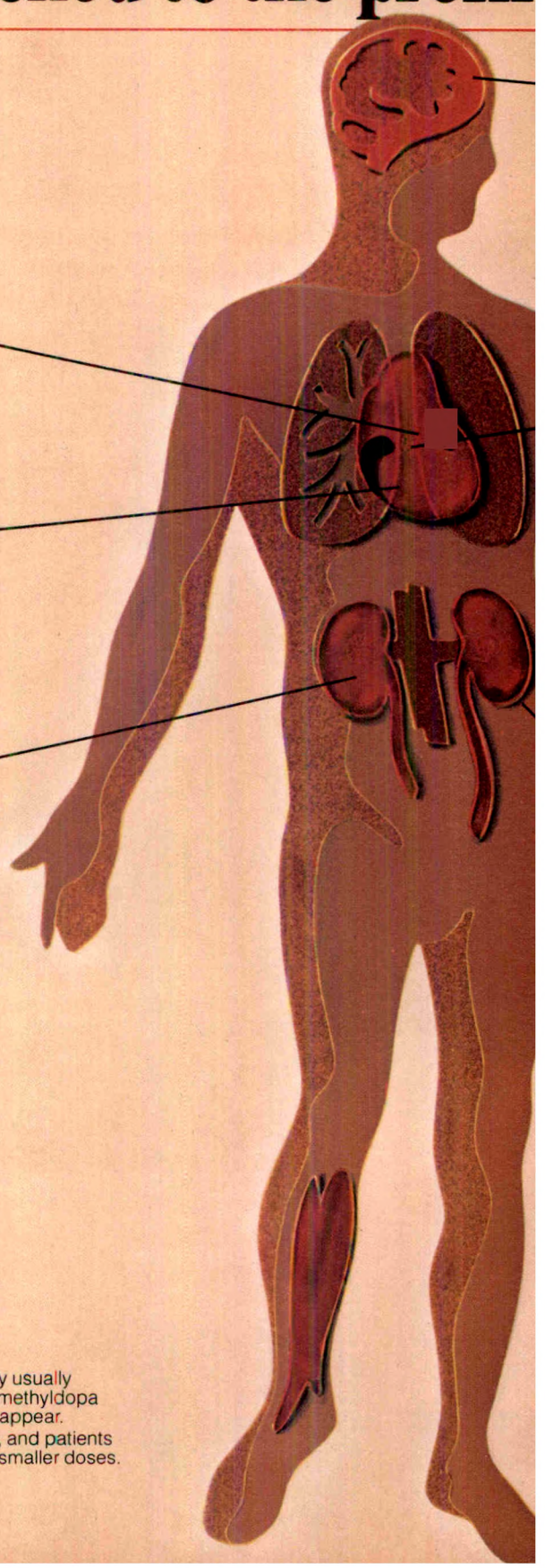
ALDOMET usually does not interfere with the cardiovascular response to exercise.

renal function often diminished

ALDOMET usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction.†

compliance often a problem

ALDOMET provides b.i.d. dosage convenience for many patients.



*Edema (and weight gain) may occur and may usually be relieved by use of a diuretic. Discontinue methyldopa if edema progresses or signs of heart failure appear.

†Methyldopa is largely excreted by the kidney, and patients with impaired renal function may respond to smaller doses.

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# of a wide range of older hypertensives

ability to autoregulate cerebral blood flow with postural changes often decreased

With ALDOMET® (Methyldopa, MSD), symptomatic postural hypotension is infrequent. Syncope in older patients may be avoided by lower doses.

cardiac output and heart rate usually normal

ALDOMET has no direct effect on cardiac function, and cardiac output usually is maintained.

total peripheral resistance usually high

ALDOMET lowers blood pressure, apparently by lowering total peripheral resistance.

ongoing therapy usually required

ALDOMET has demonstrated a high degree of efficacy in long-term therapy.

plasma renin activity usually low but may be normal or high

With ALDOMET, normal or elevated plasma renin activity may decrease.

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, or if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed.

Syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease. This may be avoided by lower doses.

MSD
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For a Brief Summary of Prescribing Information, please see following page.

ALDOMET® (MethyldopaIMSD)

Tablets, containing 125, 250, or 500 mg methyldopa; Oral Suspension, containing 250 mg methyldopa per 5 ml and alcohol 1%.

Contraindications: Active hepatic disease: such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions. With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood. At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients. Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient, dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements, psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, prolonged carotid sinus hypersensitivity, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, colitis, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Bone marrow depression, leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Dermatologic:* Rash as in eczema or lichenoid eruption; toxic epidermal necrolysis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, hyperprolactinemia, amenorrhea, impotence, decreased libido, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486

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FROM THE EDITOR

Reviewing Manuscripts: Occasionally a Test of Character

One of the least appreciated tasks performed by members of the medical academic community is their objective review of manuscripts submitted to them by the editors of medical journals. Although occasionally a reviewer may be able to evaluate a manuscript in only a few minutes, most reviews require much longer.

Reviewing a manuscript can sometimes be a test of character. A manuscript sent to a reviewer often concerns a subject about which the reviewer himself has contributed information previously, or a subject he is currently investigating or planning to investigate. Thus, the reviewer may be asked to evaluate work done by someone else on a subject of personal interest to himself. In this situation the reviewer and reviewee might well be described as competitors. Furthermore, the reviewer is asked not only to evaluate the author's work but also to provide suggestions for improving it free of charge. Medicine and science appear to be the only areas in which competitors consult one another for free advice. Can you imagine Ford Motor Company asking General Motors Corporation to provide suggestions for improving the quality of a newly designed automobile—without remuneration? Occasionally a reviewer may be asked to evaluate the manuscript of an author for whom he has no fondness, either for professional or personal reasons, or conversely, to evaluate the manuscript of an author for whom he has a high personal regard. In either of these cases the reviewer may be less than objective and the review less than ideal.

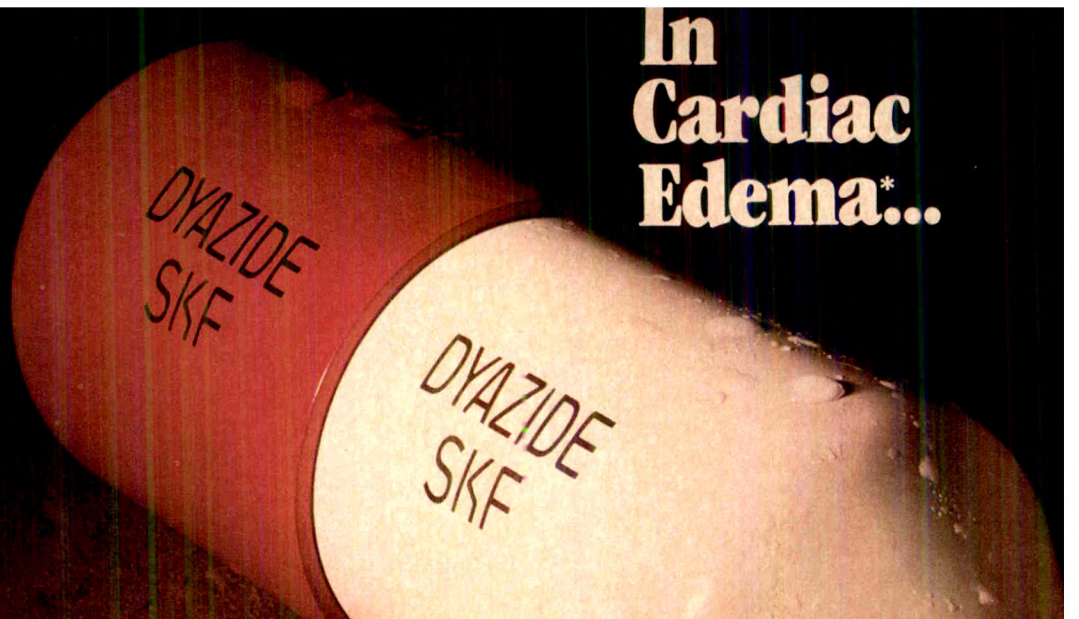
Detecting prejudice (conscious or otherwise) in a review is a continuing challenge for an editor. To help meet this challenge, I have requested that authors submitting manuscripts to the *AJC* (see the *From the Editor* column, July 1982 issue, page A3) provide in the covering letter names of potentially objective and nonobjective reviewers so that predictable or possible conflicts might be avoided.

In this professionally competitive and human atmosphere in which we all reside, the consistently objective reviewer deserves our appreciation and admiration.

William C. Roberts

William C. Roberts, MD
Editor-in-Chief

In Cardiac Edema*...



Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Dyazide® is a trademark of SK&F Co.

When You Need to Conserve K^+

SK&F CO.
a SmithKline company
Carolina, P.R. 00630

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone; restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, Dyazide should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with Dyazide. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. Dyazide interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and Dyazide should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on Dyazide, although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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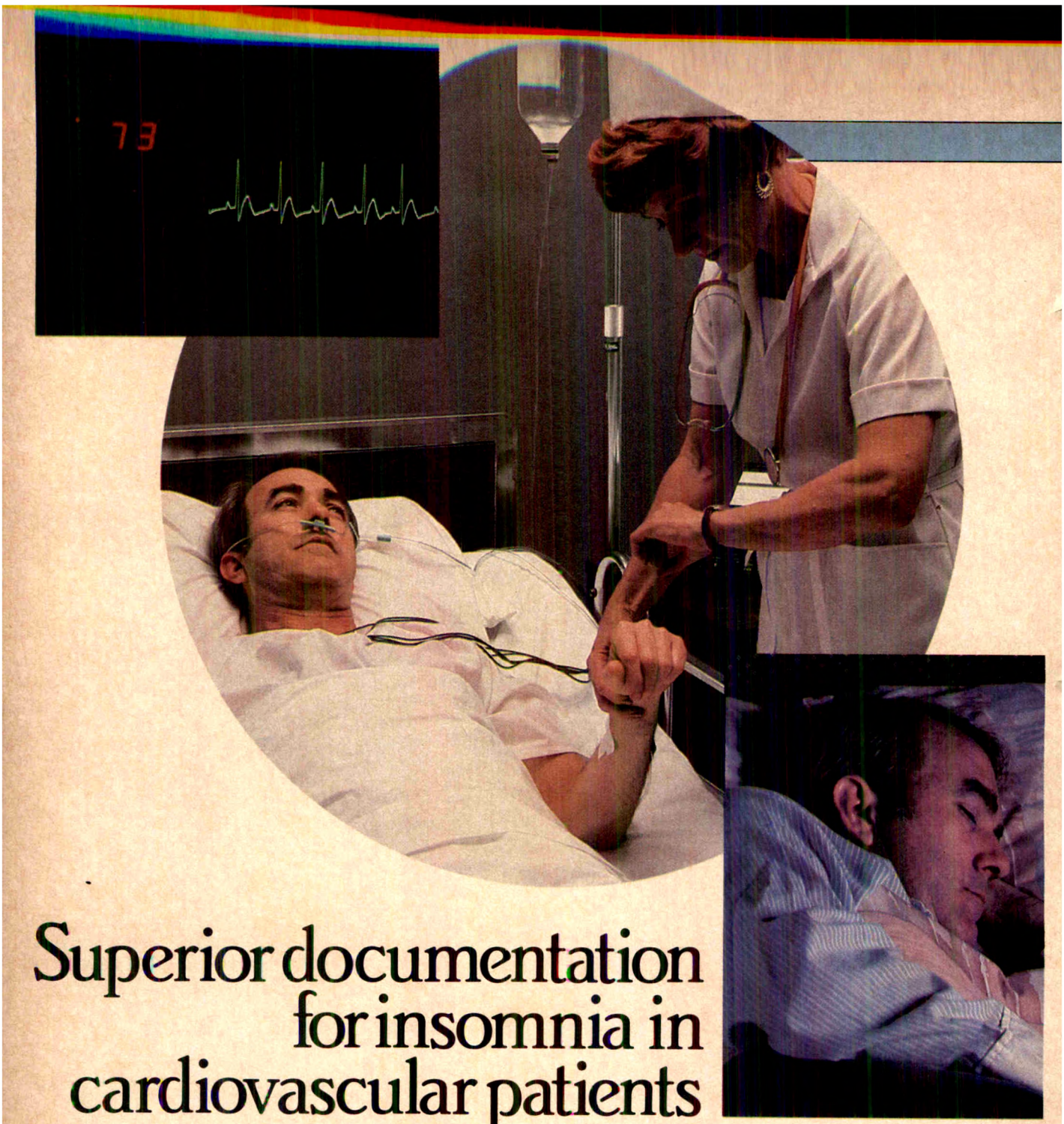

Superior documentation for insomnia in cardiovascular patients

Involving 865 hospitalized patients with cardiovascular conditions

Arteriosclerosis. Hypertension. Congestive heart failure. Myocardial infarction. Cardiac ischemia. Angina pectoris. In these and other cardiovascular conditions, insomnia is frequently a concomitant problem. While primary therapy for the medical condition is paramount, a specific hypnotic to help the patient sleep may be desirable. When needed, the hypnotic most often selected by physicians is Dalmane (flurazepam HCl/Roche).

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ROCHE®

In clinical trials, Dalmane was used to induce and maintain sleep in 865 insomniacs with concurrent cardiovascular disease.[1] In addition, a retrospective analysis of Dalmane use in 2542 hospitalized patients, 28% (over 700) of whom were admitted for treatment of cardiovascular disease, showed that Dalmane is an effective hypnotic to use in cardiovascular patients. The vast majority of patients treated with Dalmane showed a satisfactory response.[2] To preclude the risk of oversedation, dizziness and/or ataxia, dosage should be limited to 15 mg in elderly or debilitated patients.

Low incidence of morning hangover

Only 3.1% of all 2542 patients had an adverse reaction to Dalmane—the most frequent being drowsiness, confusion or ataxia.[2] (For other side effects that may occur, see Adverse Reactions in complete product information.) Caution patients about driving, operating hazardous machinery or drinking alcohol during therapy.

Patients slept sooner, longer and through the night—with no reports of rebound insomnia

Objective sleep laboratory studies have consistently demonstrated the efficacy of Dalmane in insomnia. In 8 of 8 studies Dalmane significantly reduced sleep latency in insomniacs. In 6 of 7 studies Dalmane significantly reduced wake time after sleep onset and in 5 of 6 studies Dalmane significantly reduced the number of nocturnal awakenings. Total sleep time increased significantly in 5 of 6 studies, and there were no reports of rebound insomnia, a significant worsening of insomnia after therapy discontinues.[3]

No interference with chronic warfarin therapy or chemical interference with routine laboratory tests

Dalmane does not cause an unacceptable fluctuation in prothrombin time, so it can be used safely in patients on oral anticoagulant therapy (warfarin).[4] And Dalmane does not chemically interfere with results of 22 routine laboratory tests—including SGOT, BUN, creatinine, triglycerides, cholesterol, uric acid, glucose, etc.[5] (See Adverse Reactions for alterations due to pharmacological interference.)

For documented efficacy...

Dalmane® (IV)

flurazepam HCl/Roche

15-mg/30-mg capsules

stands apart

See next page for references and summary of product information.

References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Greenblatt DJ *et al: Clin Pharmacol Ther* 21:335-361, Mar 1977. 3. Monti JM: *Methods Find Exp Clin Pharmacol* 3:303-326, May 1981. 4. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 5. Moore JD, Weissman L: *J Clin Pharmacol* 16:241-244, May-Jun 1976.

Dalmane® (IV)

flurazepam HCl/Roche

15-mg/30-mg capsules

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.

Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patient to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg recommended initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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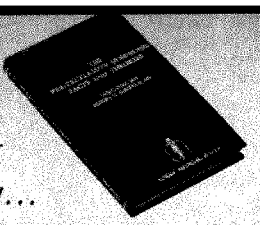
Announcing the comprehensive study of...the most fascinating syndrome in Cardiology...



THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC

Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC

Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—indeed, *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons why this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals.

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CORRECTION

In the September issue on page 475 (Gang ES, Bigger JT Jr, Livelli FD Jr: A Model of Chronic Ischemic Arrhythmias: The Relation Between Electrically Inducible Ventricular Tachycardia, Ventricular Fibrillation Threshold and Myocardial Infarct Size), the first sentence should read as follows: "Stimulation was limited to the right ventricle, a site from which most (80 to 90 percent) ventricular tachycardias can be induced in the clinical setting of a previous myocardial infarction.[5]"

Baseline anginal therapy simplified

Approximately 75% of angina patients were successfully controlled on the starting dosage—one Transderm-Nitro 5

Once-daily application of Transderm-Nitro was shown to provide effective 24-hour baseline therapy in the step-care approach to angina in a survey* of over 1,000 physicians with more than 10,000 patients under treatment.

Orthostatic hypotension may indicate nitroglycerin overdosage; reduce dosage if symptoms occur. Nitrates are contraindicated in patients with increased intraocular pressure. Withdrawal should be gradual if treatment is terminated. Do not apply to distal parts of the arms and legs.

For full details, please see the Prescribing Information on the next page.

*Data on file, CIBA Pharmaceutical Company.

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the pioneer in
transdermal therapeutics

Transderm®-Nitro
nitroglycerin

one 10-second application
provides 24-hour anginal protection.

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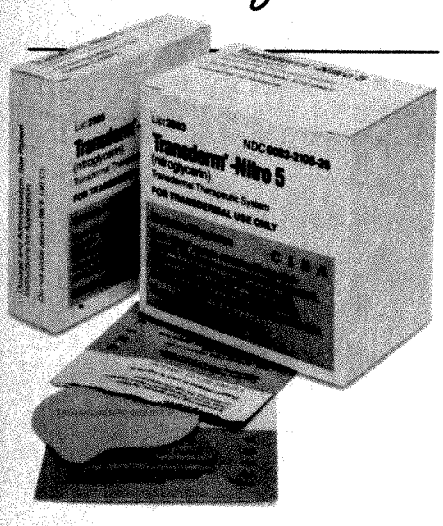


629-3688-A

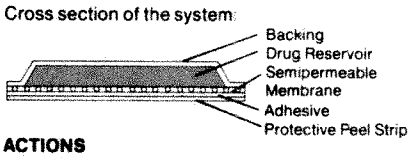
Transderm®-Nitro (nitroglycerin)
Transdermal Therapeutic System

DESCRIPTION
Transderm-Nitro (nitroglycerin) transdermal therapeutic system is a flat unit designed to provide controlled release of nitroglycerin through a semipermeable membrane continuously for 24 hours following application to intact skin. Nitroglycerin (glyceryl trinitrate) is a prompt-acting vasodilator for the relief and prevention of anginal attacks. Systems are rated to release *in vivo* 5 and 10 mg nitroglycerin over 24 hours and are in sizes of 10 and 20 cm^2 respectively.

One-fifth of the total nitroglycerin in the system is delivered transdermally to the patient over 24 hours; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. The rated release of drug is dependent upon the area of the system; 0.5 mg nitroglycerin is delivered *in vivo* for every cm^2 of system size.

The Transderm-Nitro system comprises four layers as shown below. Proceeding from the visible surface towards the surface attached to the skin, these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid; 3) an ethylene/vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Cross section of the system:



ACTIONS
When the Transderm-Nitro system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In clinical studies transdermal absorption of nitroglycerin from a nitroglycerin system occurred in a continuous and well-controlled manner, for a minimum of 24 hours. Therapeutic effect can be anticipated 30 minutes after application of the system and to be maintained for 30 minutes after its removal.

INDICATIONS AND USAGE
Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring. In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist, the dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response.

The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.

Do not store above 86°F (30°C).

PATIENT INSTRUCTIONS FOR APPLICATIONS
A patient leaflet is supplied with the systems.

HOW SUPPLIED

Transderm-Nitro System Rated Release *in vivo*	Total Nitroglycerin in System	System Size	Carton Size
5 mg/24 hr	25 mg	10 cm^2	30 Systems (NDC 0083-2105-26)
5 mg/24 hr	25 mg	10 cm^2	7 Systems (NDC 0083-2105-07)
10 mg/24 hr	50 mg	20 cm^2	30 Systems (NDC 0083-2110-26)

C82-16 (3/82)

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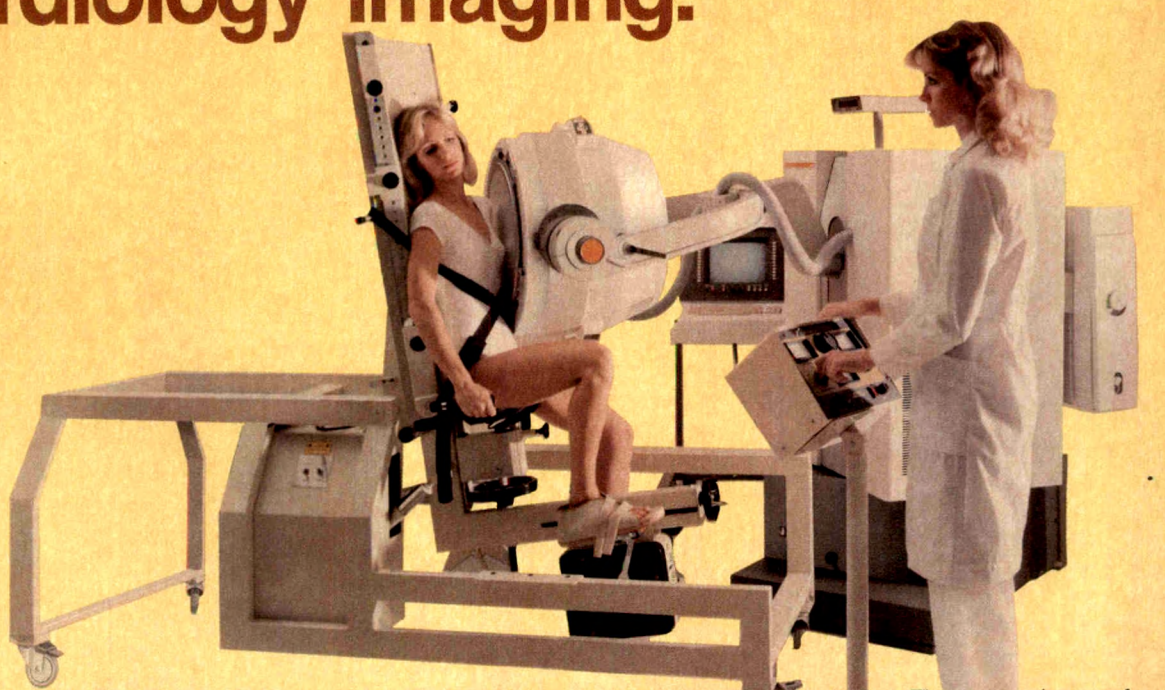

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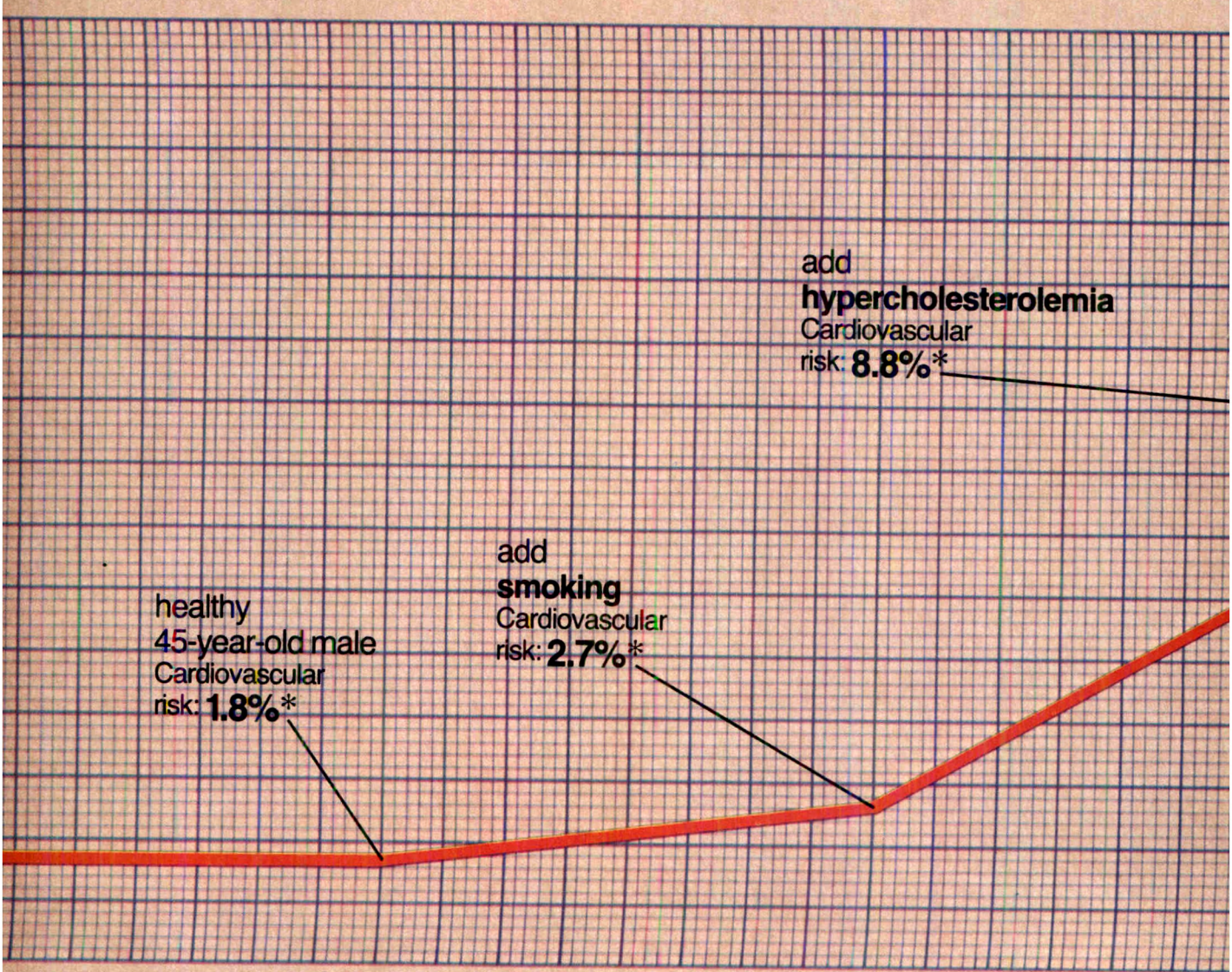
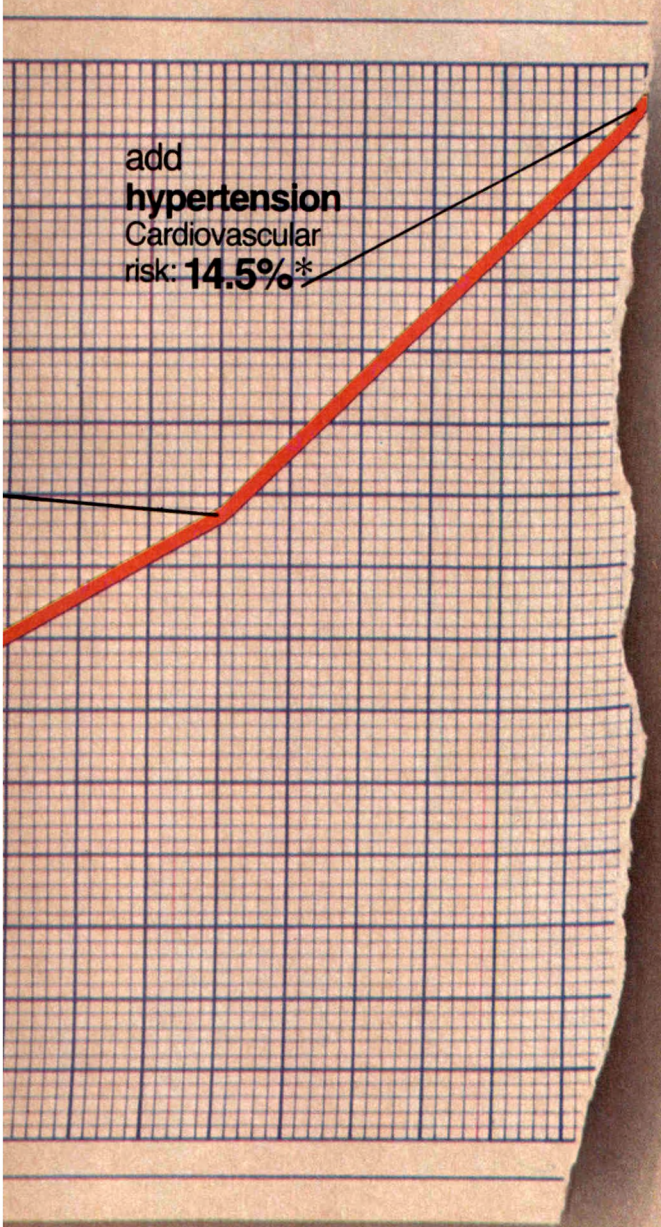


Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

*Percent equals chances in 100 of developing coronary heart disease within 6 years.

Adapted from *Coronary Risk Handbook:* Estimating risk of coronary heart disease in daily practice. 1973, American Heart Assoc., Inc.

Consider the Risks



▪ When selecting antihypertensive therapy, clinical consideration should be given to the effects of the specific drug on coronary risk factors. Blood pressure control should be achieved without adversely affecting blood lipids.

Minipress Effectively Controls Hypertension Without Adverse Effect on Blood Lipids†

▪ Minipress effectively treats hypertension. Patients have benefited from the effectiveness of Minipress in over 5 years of clinical use in this country.[1-5]

▪ Minipress has been shown not to have an adverse effect on blood lipids, according to The Oslo Study and other reports.[6-9] Because Minipress lowers high blood pressure and does not produce lipid changes which are potentially atherogenic, it provides your patient with a net reduction in risk.

†Minipress is not indicated for the treatment of hyperlipidemia.

Please see Minipress brief summary on following page.

Minipress®
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

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Minipress® (prazosin HCl) Capsules 1mg 2mg 5mg

B.I.D. Dosage Convenience

BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established.)

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus, alopecia, lichen planus.

Genitourinary: urinary frequency, incontinence, impotence, priapism.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings.)

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

References: 1. O'Conner DJ, Preston RA, Sasso EH: Renal perfusion changes during treatment of essential hypertension: Prazosin versus propranolol. *J Cardiovasc Pharmacol* 1(suppl):S38-S42, 1979. 2. Falase AO, Salako LA: The effect of prazosin combined with a diuretic, polythiazide, in hypertensive Africans. *Curr Ther Res* 25:10-15, 1979. 3. Okun R, Maxwell M: Long-term antihypertensive therapy with prazosin plus a diuretic. *J Cardiovasc Pharmacol* 1(suppl):S21-S27, 1979. 4. Kirkendall WM, Hammond JJ, Thomas JC, et al: Prazosin and clonidine for moderately severe hypertension. *JAMA* 240 (23): 2553-2556, December 1, 1978. 5. Harter HR, Delmez JA: Effects of prazosin in the control of blood pressure in hypertensive dialysis patients. *J Cardiovasc Pharmacol* 1(suppl):S43-S55, 1979. 6. Leren P, Foss PO, Helgeland A, et al: Effect of propranolol and prazosin on blood lipids: The Oslo study. *Lancet* 4-6, July 5, 1980. 7. Lowenstein J, Neusy A-J: The biochemical effects of antihypertensive agents and the impact on atherosclerosis. *J Cardiovasc Pharmacol* 4 (suppl 2):S262-S264, 1982. 8. Kokubu T, Itoh I, Kurita H, et al: Effect of prazosin on serum lipids. *J Cardiovasc Pharmacol* 4 (suppl 2):S228-S232, 1982. 9. Velasco M, Silva H, Morillo J, et al: Effect of prazosin on blood lipids and on thyroid function in hypertensive patients. *J Cardiovasc Pharmacol* 4 (suppl 2):S225-S227, 1982.

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*Test data available upon request.
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NOVEMBER 1982

The American Journal of CARDIOLOGY®

VOLUME 50

NUMBER 5

CONTENTS

CLINICAL STUDIES

933 Intracoronary Thrombolysis in Acute Myocardial Infarction: Duration of Ischemia as a Major Determinant of Late Results After Recanalization

FRANZ SCHWARZ, GERHARD SCHULER, HUGO KATUS, MANFRED HOFMANN, JOACHIM MANTHEY, HARALD TILLMANNS, HELMUTH C. MEHMEL, and WOLFGANG KÜBLER

The effect of the duration of myocardial ischemia on the late results after successful thrombolysis was assessed in 39 patients with acute transmural myocardial infarction. Patients with successful recanalization of the infarct vessel and a time lag between onset of symptoms and reperfusion less than 4 hours were assembled in group A1, and patients with recanalization but a time lag of more than 4 hours comprised group A2. Group B consisted of patients with unsuccessful thrombolysis. Before intervention the groups were comparable with regard to Gensini score of infarct vessel, regional ejection fraction of infarct area, and serum creatine kinase activity. Four weeks after the intervention patients in group A1 had a higher regional ejection fraction of infarct area than patients in groups A2 and B. Peak serum creatine kinase activity was lower in group A1 than in groups A2 and B. Thus, infarct size was reduced after early as compared with late reperfusion.

938 Sulfinpyrazone Decreases Epinephrine-Induced Platelet Aggregation After Myocardial Infarction

JEAN-GILLES LATOUR, PIERRE THEROUX, and MARTIAL G. BOURASSA

Platelet studies were performed during the course of a controlled randomized double-blind clinical trial of sulfinpyrazone in 41 patients who had a recent myocardial infarction. Aggregation of platelet-rich plasma by thrombin, collagen, adenosine diphosphate, and adrenaline was estimated 2 weeks after myocardial infarction and 6, 12, and 24 months later. At the last visit, washed platelet suspensions were also tested for aggregation to thrombin (± epinephrine) and the production of malonyldialdehyde estimated. A reduction (50%, $p < 0.02$) of the aggregation of platelet-rich plasma to epinephrine and a milder ($p < 0.01$) potentiation by the catecholamine of aggregation by thrombin of the washed platelet suspensions were found in the group treated with sulfinpyrazone as compared with the placebo group. Other assays were not useful in discriminating between the 2 groups. It is concluded that sulfinpyrazone (200 mg 4 times daily) normalizes the platelet response to epinephrine.

945 Familial Aggregation of Coronary Heart Disease and Its Relation to Known Genetic Risk Factors

LEO P. ten KATE, HELGE BOMAN, STEPHEN P. DAIGER, and ARNO G. MOTULSKY

Familial aggregation of coronary heart disease in the Pacific Northwest could not be explained by familial clustering of known genetic risk factors such as hypertension, hyperlipidemia, and diabetes. In families with coronary heart disease the risk of myocardial infarction was still twice that of control subjects after statistical manipulation had eliminated the role of these genetic factors. Such unexplained familial aggregation could be caused by various shared environmental factors, by yet undefined genetic factors, or by interaction of unspecified genes with the environment.

954 Assessment of Vasodilator Therapy in Patients With Severe Congestive Heart Failure: Limitations of Measurements of Left Ventricular Ejection Fraction and Volumes

BRIAN G. FIRTH, GREGORY J. DEHMER, ROY V. MARKHAM, Jr., JAMES T. WILLERSON, and L. DAVID HILLIS

This study was performed to assess the relation between changes in left ventricular (LV) volumes and ejection fraction (determined scintigraphically) and changes in intracardiac pressures and forward cardiac index (by thermodilution) in response to administration of sodium nitroprusside in 12 patients with severe, chronic congestive

Continued on Page A25

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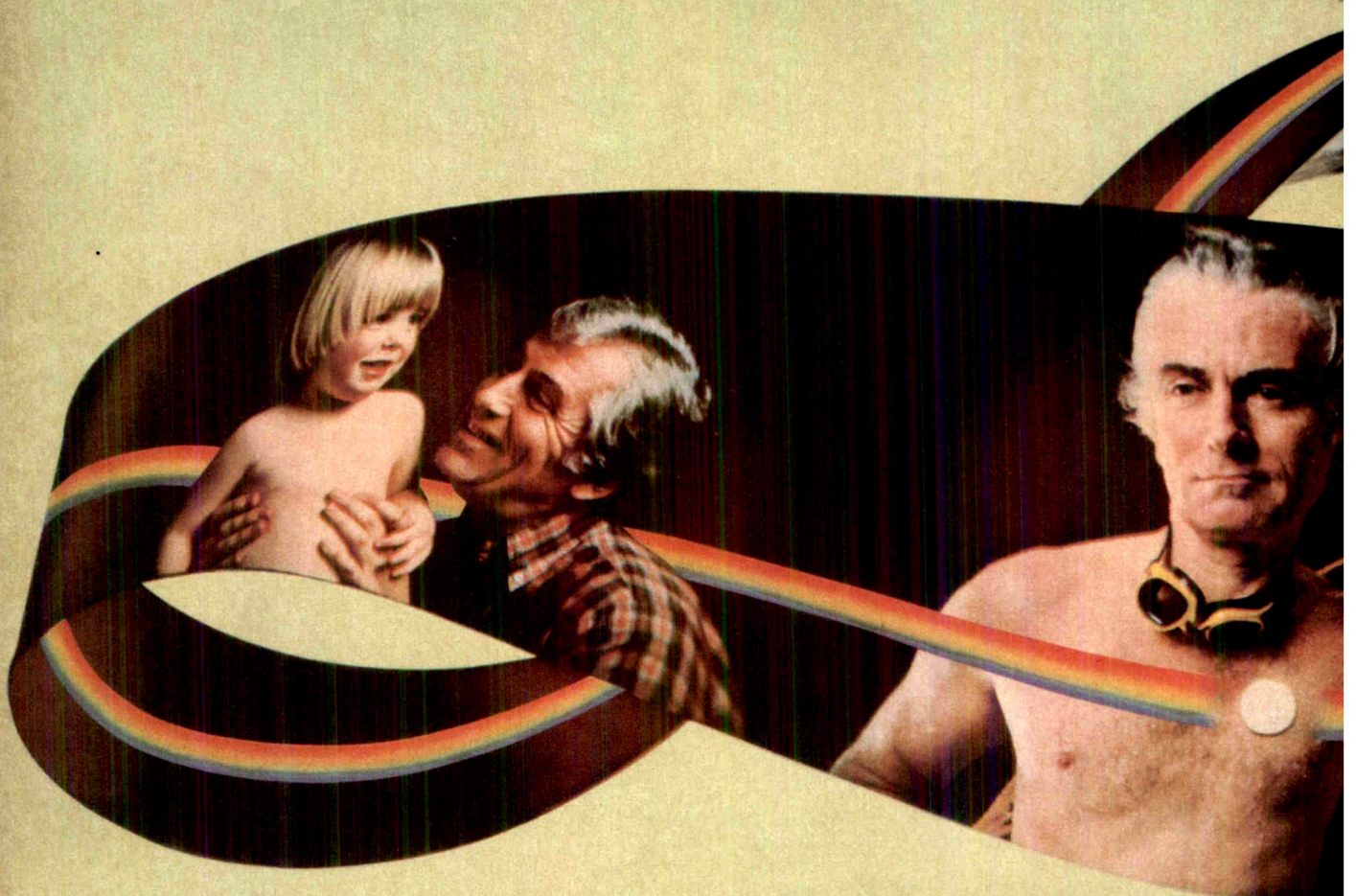
NITRODISC™

(nitroglycerin) 5-MG/24-HR; 10-MG/24-HR PAD

Continuous anginal



Contraindications for nitroglycerin include patients with increased intraocular pressure. Side effects include headache, hypotension, flushing, and dizziness. In terminating treatment, both the dosage and frequency of application must be gradually reduced during a period of four to six weeks.

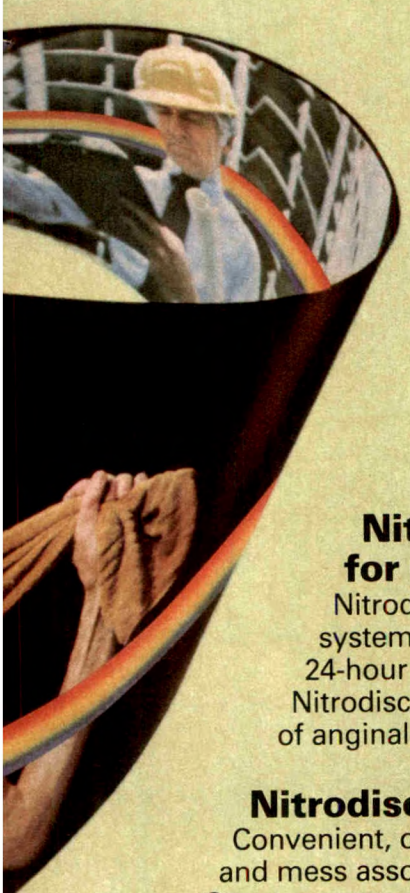
protection...q.d.

Preliminary results from a clinical study indicate 24-hour improvement in exercise capacity

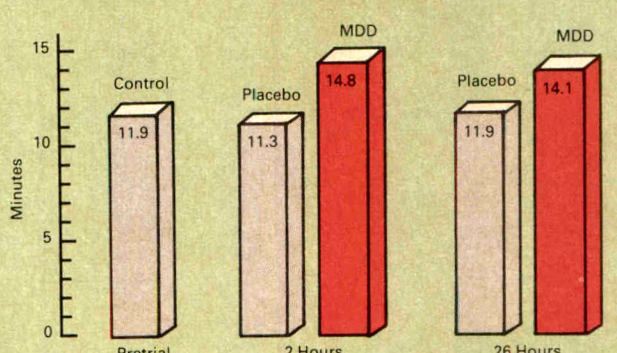
Until now, the clinically recognized benefits of a single nitrate dose have not been documented beyond 12 hours.

In a controlled study,[1] Searle's new nitroglycerin Microseal Drug Delivery™ (MDD) system provided an 18% average increase in exercise capacity 26 hours after application.[2]

In addition, the need for sublingual nitroglycerin was reduced.



Mean Exercise Duration



Nitrodisc (nitroglycerin) eliminates the need for multiple doses of long-acting oral nitrates

Nitrodisc's unique solid polymer releases nitroglycerin into the systemic circulation at a controlled and sustained rate over a 24-hour period.

Nitrodisc (nitroglycerin) is not intended for the immediate relief of anginal attacks.

Nitrodisc enhances compliance

Convenient, once-daily dosage schedule, plus the absence of bother and mess associated with nitroglycerin ointments.

Secure, waterproof adhesive allows for a complete range of daily activities.

1 The interim results presented include data on eight patients completing the protocol to date. A total of twenty patients will be included.

2 Thompson RH: Clinical use of transdermal delivery devices with nitroglycerin. Presented at the Medical Therapy for Angina in the 1980s: New Horizons Symposium, Atlanta, April 24, 1982.

In another clinical study conducted among cardiac rehabilitation participants, concomitant Nitrodisc (nitroglycerin) propranolol therapy did not demonstrate a significant improvement over propranolol alone.

Please see the following page for the complete prescribing information.

SEARLE

5-MG/24-HR; 10-MG/24-HR

NITRODISC™
(nitroglycerin)

DESCRIPTION: The Nitrodisc pad incorporates a patented Microseal Drug Delivery™ system consisting of a solid, nitroglycerin-impregnated polymer bonded to a flexible, non-sensitizing adhesive bandage. It is designed to be applied topically. Nitrodisc provides constant and controlled drug delivery over a uniform skin surface area for 24 hours.

Nitrodisc is available in two strengths that release either 5 mg or 10 mg of nitroglycerin during a 24-hour period. The 5 mg/24 hr system contains 16 mg nitroglycerin over an 8 cm^2 releasing surface. The 10 mg/24 hr system contains 32 mg nitroglycerin over a 16 cm^2 releasing surface (see HOW SUPPLIED section).

ACTIONS: When a Nitrodisc pad is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart and peripheral vasculature) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is due to a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In addition, a direct effect of nitroglycerin on the coronary vessels is recognized as well.

In clinical studies, transdermal absorption of nitroglycerin from Nitrodisc occurred in a continuous and well-controlled manner for a minimum of 24 hours. Therapeutic plasma levels were attained within 1 hour after the application of the pad and remained in the therapeutic range for 24 hours. Plasma levels of nitroglycerin were still detectable 30 minutes after removal of the system.

The amount of nitroglycerin released (5 mg/24 hr or 10 mg/24 hr) represents the mean absorption rates through skin determined during clinical evaluations. Absorption may vary among individuals.

INDICATIONS AND USAGE: Nitrodisc is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Nitrodisc (nitroglycerin) is contraindicated in patients known to be intolerant of organic nitrate drugs, and in patients with marked anemia, increased intraocular pressure, or increased intracranial pressure.

WARNINGS: In patients with acute myocardial infarction or congestive heart failure, Nitrodisc should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of patients with angina, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent potential withdrawal reactions, which are characteristic of all vasodilators in the nitrate class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness, or dizziness, particularly orthostatic hypotension, may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Nitrodisc is not intended for immediate relief of anginal attacks. For this purpose, occasional use of sublingual preparations may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Nitrodisc therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist, Nitrodisc (nitroglycerin) dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION: A Nitrodisc pad should be applied once each day. To use the pad, follow the instructions on the package. Nitrodisc should be applied to a skin site free of hair and not subject to excessive movement. It should not be applied to the distal parts of the extremities. A suitable area should be shaved free of hair, if necessary. The application site should be changed slightly each time to avoid undue skin irritation. A new pad should be applied if the product loosens.

The optimal dosage regimen should be selected based upon the clinical response, the side effects, and the effects of therapy upon blood pressure and heart rate. It is recommended that therapy be initiated with the smaller pad, and that the larger pad be utilized when a greater response is desired. In the event that higher doses are necessary, multiple pads may be applied.

PATIENT INSTRUCTIONS FOR APPLICATION: These are provided with the product.

HOW SUPPLIED:

Nitrodisc	5 mg/24 hr	10 mg/24 hr
Drug released per 24 hours	5 mg	10 mg
Total drug content	16 mg	32 mg
Drug releasing surface	8 cm^2	16 cm^2

Nitrodisc pads are supplied in cartons of 30. Store at a controlled room temperature of 59°-86°F (15°-30°C). **Do not refrigerate.** Extremes of temperature and humidity should be avoided.

SEARLE *Searle Pharmaceuticals Inc. Box 5110, Chicago, IL 60680*

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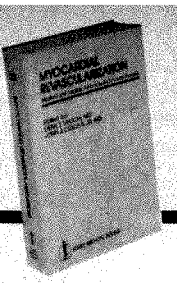

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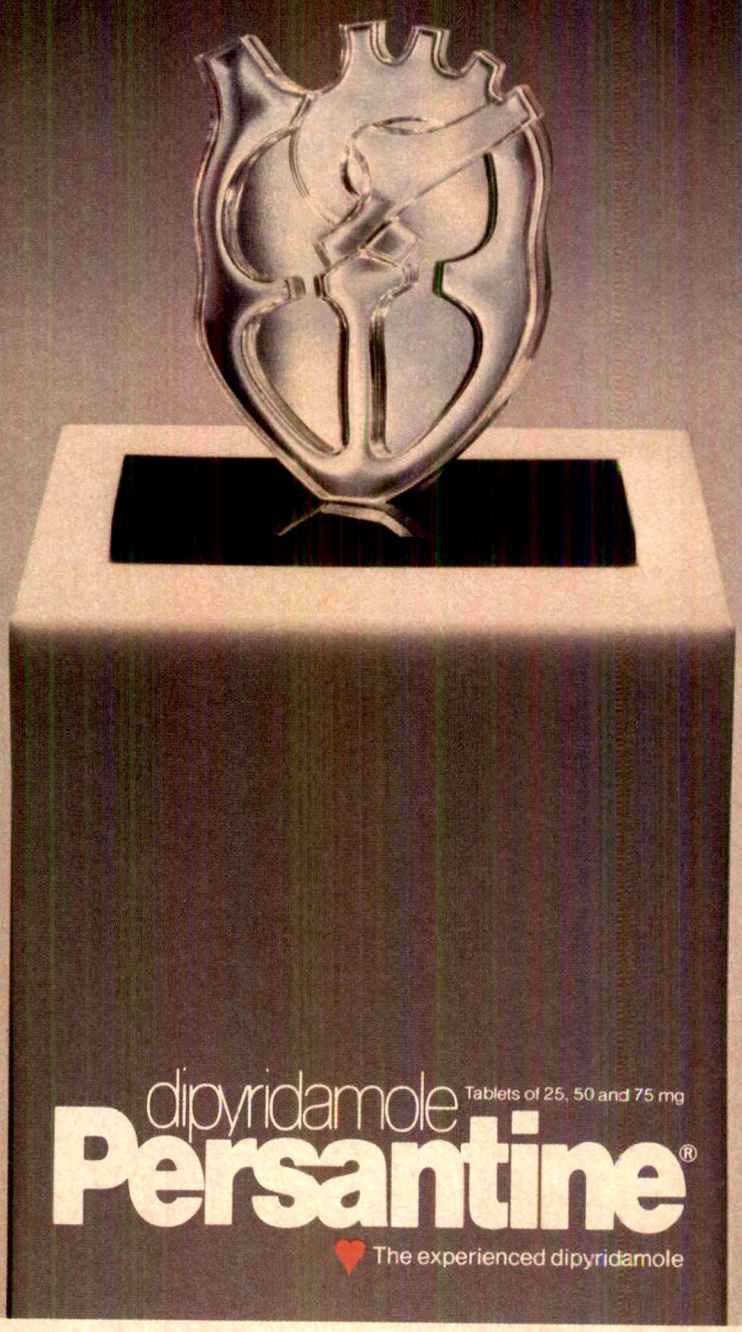

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heart failure and markedly dilated left ventricles. Nitroprusside caused a decrease in mean systemic arterial, pulmonary arterial, and pulmonary capillary wedge pressures and an increase in the forward cardiac index; simultaneously LV end-diastolic and end-systolic volume indexes decreased. The only significant correlation between scintigraphically and invasively determined variables was between the percent change in the LV end-diastolic volume index and the percent change in pulmonary capillary wedge pressure ($r = 0.68$; $p = 0.01$). Despite this correlation, the percent change in pulmonary capillary wedge pressure was a considerably more sensitive index of the change produced than the percent change in LV end-diastolic volume index.

960 Effects of Acute and Chronic Minoxidil Administration on Rest and Exercise Hemodynamics and Clinical Status in Patients With Severe, Chronic Heart Failure

MARK NATHAN, STANLEY A. RUBIN, DEIRDRE SIEMIENCZUK, and H.J.C. SWAN

The vasodilator properties of minoxidil were investigated in 10 patients with severe chronic heart failure. Short-term evaluation of resting and exercise hemodynamics showed a 40% increase in resting and a 30% increase in exercise cardiac output due to increases in stroke volume. There was little change in intracardiac pressure or arterial pressure, although marked decreases were noted in a few patients. Systemic vascular resistance decreased in patients receiving minoxidil. Short-term adverse effects included development of unstable angina in 1 patient. Five week follow-up showed substantial clinical improvement in 5 patients. However, peripheral edema developed in all patients; even an increase in diuretic drugs did not satisfactorily control edema in all patients. Minoxidil may be a useful afterload reduction agent in some patients with heart failure. Well-known side effects in outpatients may limit its utility.

967 Coronary Hemodynamic Effects of Angiotensin Inhibition by Captopril and Teprotide in Patients With Congestive Heart Failure

JONATHAN L. HALPERIN, DAVID P. FAXON, MARK A. CREAGER, THEODORE A. BASS, CAROLINE D. MELIDOSSIAN, HARALAMBOS GAVRAS, and THOMAS J. RYAN

The coronary hemodynamic effects of vasodilator therapy with angiotensin converting enzyme inhibitors were studied in patients with ischemic heart disease and severe congestive failure. Coronary sinus thermodilution blood flow paralleled perfusion pressure but did not significantly vary overall, and coronary vascular resistance was unchanged. Although the left ventricular stroke-work index rose slightly there was no change in the coronary arteriovenous oxygen content difference or the calculated myocardial oxygen consumption. The heart rate-systolic blood pressure product declined significantly during this period; this relief of cardiac effort was a function of the pretreatment plasma renin activity. A derived index of external myocardial efficiency improved 37%, reflecting greater left ventricular work without increased oxygen demand. Enhancement of myocardial performance after converting enzyme inhibition appears dependent on reduction of angiotensin-mediated ventricular afterload and preload. The lack of coronary vasomotor effects in patients with advanced ischemic cardiomyopathy may reflect limited coronary vascular reserve. Improvement of heart failure in these patients developed without evidence of myocardial ischemia, since balance was maintained between oxygen supply and demand.

973 Accuracy of Cardiac Output, Oxygen Uptake, and Arteriovenous Oxygen Difference at Rest, During Exercise, and After Vasodilator Therapy in Patients With Severe, Chronic Heart Failure

STANLEY RUBIN, DEIRDRE SIEMIENCZUK, MARK D. NATHAN, JOANN PRAUSE, and H.J.C. SWAN

Measurement of hemodynamic and gas exchange variables may be subject to technical and biologic inaccuracies in patients with heart failure. Cardiac output was measured by thermodilution, oxygen uptake by expired gas collection, and arteriovenous oxygen content difference by spectrophotometry in 16 patients with heart failure at rest and during exercise and again after vasodilator therapy. Measured values were compared with values calculated from Fick's principle; excellent correlations were found for cardiac output (r 0.86 to 0.93), for oxygen uptake (r 0.84 to 0.95), and for arteriovenous oxygen difference (r 0.76 to 0.93). It is concluded that no substantial or systematic difference exists between directly measured and calculated values of these variables in patients with heart failure.

979 Effects of Amyl Nitrite on Left Ventricular Relaxation in Patients With Borderline Hypertension

CHARLES Z. NAGGAR, KENNETH STANLEY, and LORI L. DOWNING

Left ventricular relaxation velocity was measured echocardiographically in 22 healthy volunteers and 15 patients with borderline hypertension. The tangent to the left ventricular posterior wall endocardium was measured in diastole and normalized for end-diastolic dimension. This normalized velocity of relaxation at rest was similar

Continued on Page A29

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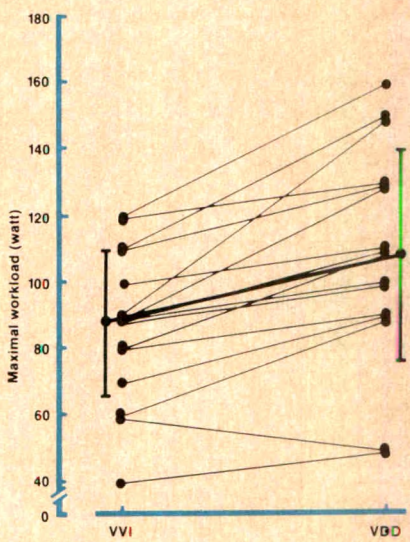

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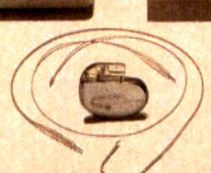

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1. This particular study was conducted by physicians Ib Kruse and Lars Ryden, Central Hospital, Skövde, Sweden.

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Precautions
The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects
Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

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in both groups. However, the normalized velocity of relaxation in the borderline hypertensive group showed a blunted response to amyl nitrite when compared with that in the normal group. Heart rate, mean arterial pressure, and fractional shortening were the best predictors of normalized velocity of relaxation. Normalized velocity of relaxation may show the earliest measurable change of myocardial dysfunction before alteration in mass or contractility are evident. The echocardiographic amyl nitrite test may prove to be a simple noninvasive tool for the detection of early involvement of cardiac muscle in hypertension.

985 Significance of Abnormal Electrocardiograms in Highly Trained Athletes

DAVID G. OAKLEY and CELIA M. OAKLEY

Electrocardiographic and other abnormalities of highly trained athletes are well recorded but not well enough known, and the more extreme changes still cause diagnostic confusion. This problem was exemplified by 10 athletes, all referred to us by cardiologists because of a diagnosis of organic heart disease. After thorough investigation, including catheter studies, all but 1 of these patients was regarded as normal and all returned to competitive sports. The criteria for diagnosing heart disease in athletes are discussed in light of the findings in these 10 patients. Exercise electrocardiography and echocardiography help to exclude organic disease, but left heart catheterization is justified when doubt still exists.

990 Nonobstructive Hypertrophic Cardiomyopathy: A Precise Assessment of Hemodynamic Characteristics and Clinical Implications

YUZO HIROTA, KOICHI FURUBAYASHI, KIYOTAKA KAKU, GEN SHIMIZU, MASAYA KINO, KEISHIRO KAWAMURA, and TADASU TAKATSU

A precise assessment of left ventricular function was performed in 20 patients with hypertrophic nonobstructive cardiomyopathy to elucidate the basic pathophysiology, and the data were compared with those in 22 normal subjects. Whereas end-diastolic pressure was high in those with cardiomyopathy, a more accurate index of preload, end-diastolic stress, did not differ from normal. Afterload was about half the normal value. Both isovolumic and ejection phase indexes of contractility were in the normal range; however, the end-systolic stress volume ratio was significantly reduced. Although the left ventricular minute work index was in the normal range, the unit muscle performance was very low. An abnormality of left ventricular relaxation was demonstrated by low peak negative dP/dt and prolonged time constant T, and a stiff left ventricle was demonstrated by a high diastolic elastic stiffness constant. These observations suggest that the contraction of a unit muscle is inappropriate to produce an adequate contraction of the whole ventricle, and that hypertrophy might be an adaptive process to maintain normal systolic function by increasing mass and reducing afterload.

998 The Heart and Cardiac Conducting System in Polymyositis-Dermatomyositis: A Clinicopathologic Study of 16 Autopsied Patients

HELEN M. HAUPT, and GROVER M. HUTCHINS

Sixteen autopsied patients with polymyositis-dermatomyositis syndromes were reviewed to determine the nature of the cardiac involvement. The adult patients were aged 32 to 84 years (average 56). There were 2 children, aged 2 and 10 years. Seven patients had congestive heart failure; 4 of these had myocarditis. Two patients had bundle branch block; 1 had myocarditis involving the conduction system. There was active myocarditis in 4 (25%), myocardial fibrosis in 4 (25%), coronary vascular changes in 5 (31%). All patients with active myocarditis had skeletal muscle involvement; 9 patients with myositis did not have myocarditis. There was no correlation of overall severity of disease with active myocarditis. The study shows that cardiac involvement may be common in polymyositis; congestive failure or conduction abnormalities arising in this setting may indicate myocarditis.

1007 Immune Reactions in Tuberculous and Chronic Constrictive Pericarditis. Clinical Data and Diagnostic Significance of Antimyocardial Antibodies

BERNHARD MAISCH, STEFANIE MAISCH, and KURT KOCHSIEK

In all patients with exudative tuberculous pericarditis (n = 12) and viral perimyocarditis (n = 10) antimyolemmal antibodies, a subtype of antisarcolemmal antibodies, were found, whereas this antibody could not be detected in patients with exudative tuberculosis of the lungs and in only 1 of the patients (n = 12) with constrictive pericarditis. Antifibrillary antibodies of the antimyosin type were missed in patients with viral heart disease but could be demonstrated in 75% of patients with tuberculous pericarditis. Sera containing high titer antimyolemmal antibodies induced cytolysis of vital adult heterologous cardiocytes, suggesting that these antibodies are both of diagnostic and pathogenetic relevance.

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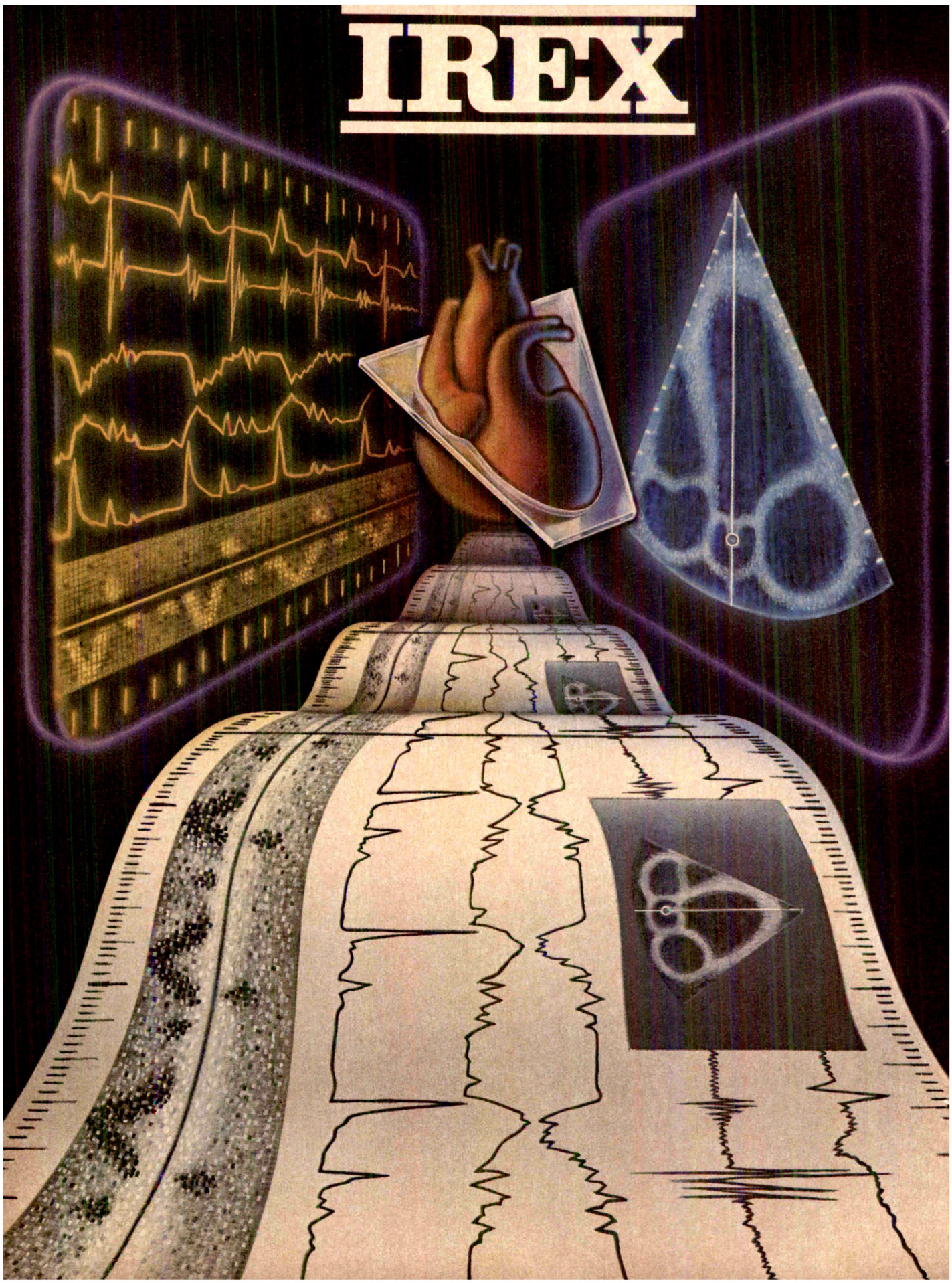
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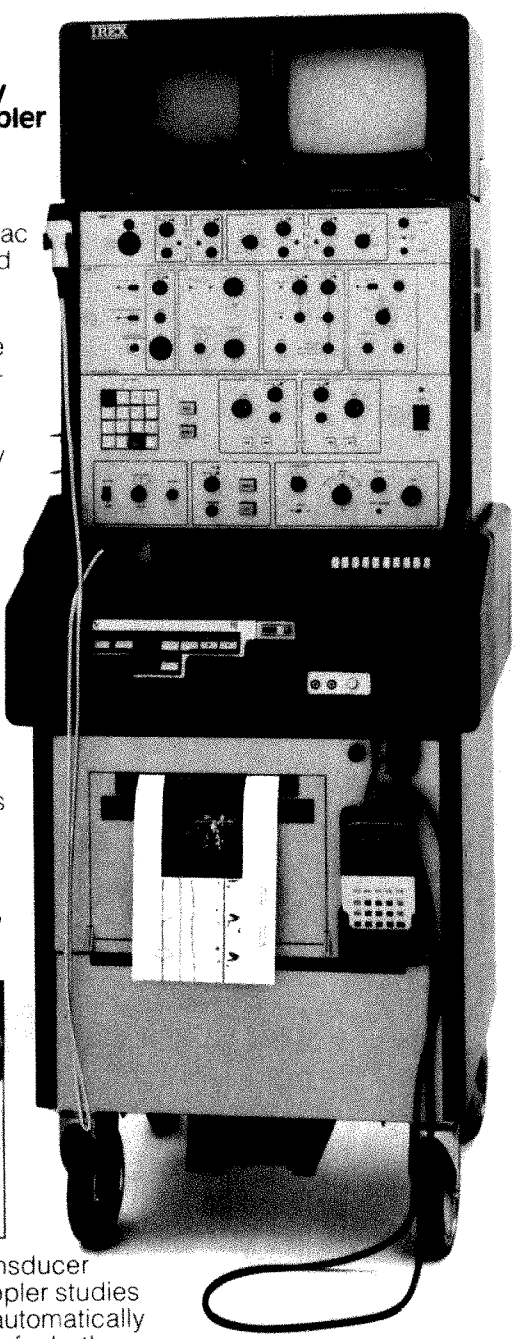

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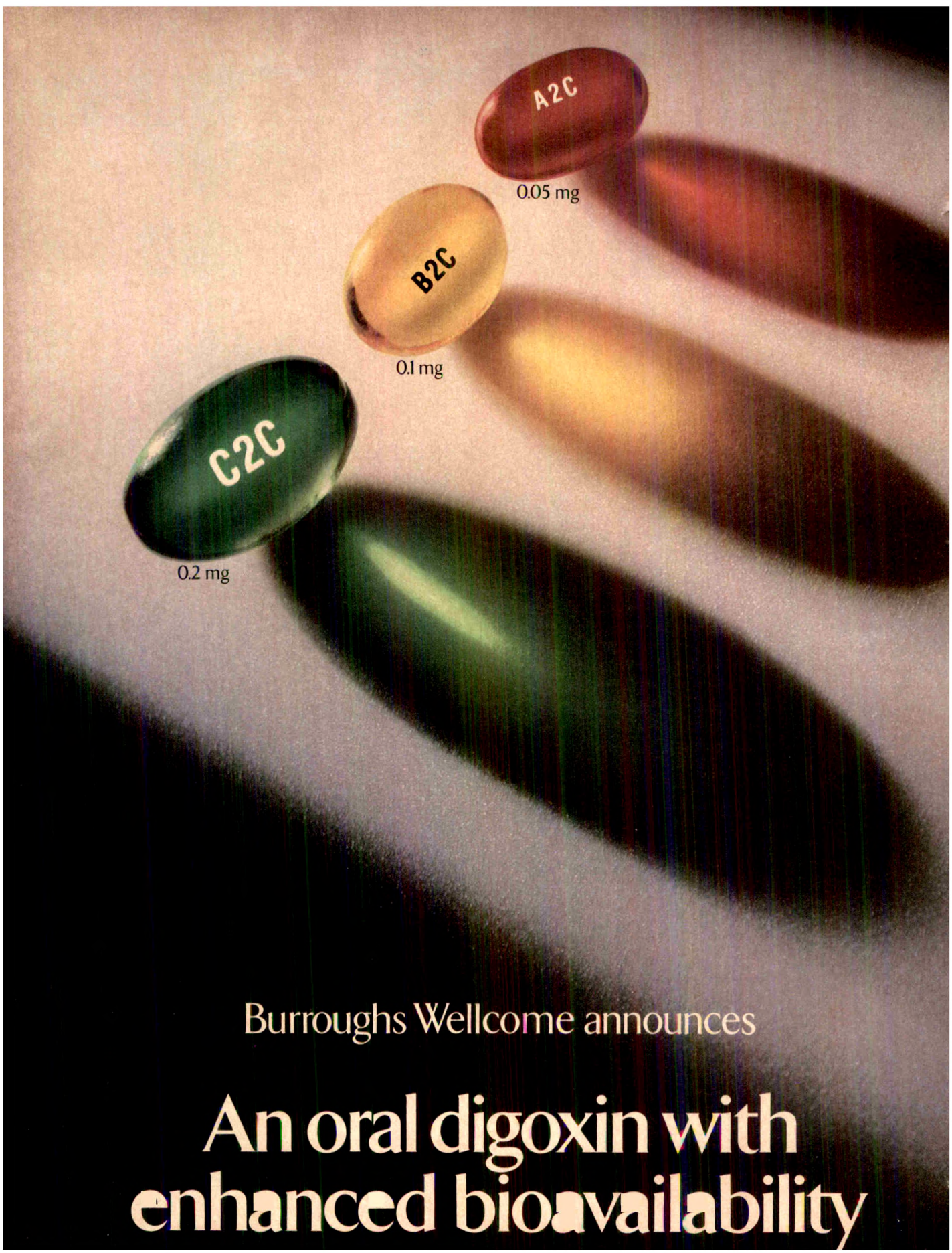

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INDICATIONS AND USAGE
Heart Failure: The increased cardiac output resulting from the inotropic action of digoxin ameliorates the disturbances characteristic of heart failure (venous congestion, edema, dyspnea, orthopnea and cardiac asthma).

Digoxin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous fistula, anemia, infection or hyperthyroidism.

Digoxin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies have shown, however, that even though hemodynamic effects can be demonstrated in almost all patients, corresponding improvement in the signs and symptoms of heart failure is not necessarily apparent. Therefore, in patients in whom digoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable renal function or whose potassium levels tend to fluctuate) a cautious withdrawal of digoxin may be considered. If digoxin is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure.

CONTRAINDICATIONS
Digitalis glycosides are contraindicated in ventricular fibrillation.

Any untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin, as is hypersensitivity to digoxin itself. Allergy to digoxin, though rare, does occur. It may not extend to all preparations, and another digitalis glycoside may be tried with caution.

WARNINGS
The use of digoxin or other digitalis glycosides is unwarranted in the treatment of obesity.

Digoxin in soft capsules should be administered in divided daily doses to minimize any potential adverse reactions. Where compliance is considered a problem, single daily dosing may be appropriate.

Anorexia, nausea, vomiting, and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section in complete prescribing information).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary. Careful monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity. Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS
General: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section in complete prescribing information). More time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range," because potassium depletion sensitizes the myocardium to digoxin. Hypokalemia may result from diuretic, amphotericin B, or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see *Treatment of arrhythmias produced by overdosage*, in OVERDOSAGE section).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypocalcemia can nullify the effects of digoxin in man; digoxin may be ineffective until serum calcium is restored to normal.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine causes a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the quinidine dose. Because of the considerable variability of this interaction, digoxin dosage should be carefully individualized.

Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (eg, hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e., sick sinus syndrome), digoxin may worsen sinus bradycardia or sinoatrial block.

In patients with Wolff-Parkinson-White syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Drug Interactions: Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias. *Quinidine* causes a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. *Antacids, kaolin-pectin, sulfasalazine, neomycin,* and *cholestyramine* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Thyroid* administration to a digitalized hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias, because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although *propranolol* and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

ADVERSE REACTIONS
The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section). The overall incidence of adverse reactions has been reported as 5% to 20%, with 15% to 20% being considered serious (1% to 4% of patients receiving digoxin). Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults:
Cardiac—Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease. Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (nodal) rhythm, and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage.

Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances.

Gastrointestinal—Anorexia, nausea, vomiting, and, less commonly, diarrhea are common early symptoms of overdosage. Uncontrolled heart failure may also produce such symptoms.

CNS—Visual disturbances (blurred or yellow vision), headache, weakness, apathy, and psychosis can occur.

Other—Gynecomastia is occasionally observed.

Infants and Children:
Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea, and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Ventricular

arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

OVERDOSAGE Treatment of arrhythmias produced by overdosage

Adults:

Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is necessary if toxic manifestations are not severe.

Potassium salts are commonly used, particularly if hypokalemia is present. Potassium chloride in divided oral doses totaling 3 to 6 grams of the salt (40 to 80 mEq K+) for adults may be given provided renal function is adequate (see below for potassium recommendations in infants and children).

When correction of the arrhythmia is urgent and the serum potassium concentration is low or normal, potassium should be administered intravenously in 5% dextrose injection. For adults, a total of 40 to 80 mEq (diluted to a concentration of 40 mEq per 500 ml) may be given at a rate not exceeding 20 mEq per hour, or slower if limited by pain due to local irritation. Additional amounts may be given if the arrhythmia is uncontrolled and potassium well tolerated. ECG monitoring should be performed to watch for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia. The infusion may be stopped when the desired effect is achieved.

Note: Potassium should not be used and may be dangerous in heart block due to digoxin unless primarily related to supraventricular tachycardia.

Other agents that have been used for the treatment of digoxin intoxication include lidocaine, procainamide, propranolol, and phenytoin, although use of the latter must be considered experimental. In advanced heart block, temporary ventricular pacing may be beneficial.

Infants and Children:

See Adults section (immediately above) for general recommendations for the treatment of arrhythmias produced by overdosage and for cautions regarding the use of potassium.

If a potassium preparation is used to treat toxicity, it may be given orally in divided doses totaling 1 to 1.5 mEq K+ per kilogram (kg) body weight (1 gram of potassium chloride contains 13.4 mEq K+).

When correction of the arrhythmia with potassium is urgent, approximately 0.5 mEq/kg of potassium per hour may be given intravenously, with careful ECG monitoring. The intravenous solution of potassium should be dilute enough to avoid local irritation; however, especially in infants, care must be taken to avoid intravenous fluid overload.

DOSAGE AND ADMINISTRATION

Recommended dosages are average values that may require considerable modification because of individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended doses.

Due to the more complete absorption of digoxin from soft capsules, recommended oral doses are only 80% of those for tablets, elixir, and IM injection.

Because the significance of the higher peak serum concentrations associated with once-daily capsules is not established, divided daily dosing is presently recommended for:

1. infants and children under 10 years of age;
2. patients requiring a daily dose of 300 μg (0.3 mg) or greater;
3. patients with a previous history of digitalis toxicity;
4. patients considered likely to become toxic;
5. patients in whom compliance is not a problem.

Where compliance is considered a problem, once-daily dosing may be appropriate.

Adults:

Adults: rapid digitalization with a loading dose—Peak body digoxin stores of 8 to 12 μg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Larger stores (10 to 15 μg/kg) are often required for adequate control of ventricular rate in patients with atrial flutter or fibrillation. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (i.e., 6 to 10 μg/kg [see PRECAUTIONS section]).

The loading dose should be based on the projected peak body stores and administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6- to 8-hour intervals, *with careful assessment of clinical response before each additional dose.*

If the patient's clinical response necessitates a change from the calculated dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

Dosage for Previously Undigitalized Patients:

In previously undigitalized patients, a single initial Lanoxicaps dose of 400 to 600 μg (0.4 to 0.6 mg) usually produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2 to 6 hours. Additional doses of 100 to 300 μg (0.1 to 0.3 mg) may be given cautiously at 6- to 8-hour intervals until clinical evidence of an adequate effect is noted. The usual amount of Lanoxicaps that a 70-kg patient requires to achieve 8 to 15 μg/kg peak body stores is 600 to 1000 μg (0.6 to 1.0 mg).

Adults: gradual digitalization with a maintenance dose—The following table provides average Lanoxicaps daily maintenance dose requirements for patients with heart failure based upon lean body weight and renal function:

Usual Lanoxicaps Daily Maintenance Dose Requirements (μg) for Estimated Peak Body Stores of 10 μg/kg

Corrected Ccr (ml/min per 70 kg)	Lean body weight (kg/lbs) 50/110	60/132	70/154	80/176	90/198	100/220	Number of days before steady-state achieved
0	50	100	100	100	150	150	22
10	100	100	100	150	150	150	19
20	100	100	150	150	150	200	16
30	100	150	150	150	200	200	14
40	100	150	150	200	200	250	13
50	150	150	200	200	250	250	12
60	150	150	200	200	250	300	11
70	150	200	200	250	250	300	10
80	150	200	200	250	300	300	9
90	150	200	250	250	300	350	8
100	200	200	250	300	300	350	7

Example—Based on the above table, a patient in heart failure with an estimated lean body weight of 70 kg and a Ccr of 60 ml/min should be given 200 μg (0.2 mg) of Lanoxicaps per day, usually taken as a 100 μg (0.1 mg) capsule after the morning and evening meals. Steady-state serum concentrations should not be anticipated before 11 days.

Digitalizing Dose for Children:

Usual Digitalizing and Maintenance Dosages for Lanoxicaps in Children With Normal *Renal Function Based on Lean Body Weight*

Age	Digitalizing* Dose (μg/kg)	*Daily*† Maintenance Dose (μg/kg)
2-5 Years	25-35	25%-35% of the oral or IV loading dose‡
5-10 Years	15-30	
Over 10 Years		

*IV digitalizing doses are the same as Lanoxicaps digitalizing doses.

†Divided daily dosing is recommended for children under 10 years of age.

‡Projected or actual digitalizing dose providing desired clinical response.

More gradual digitalization can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided above can be used in calculating this dose for patients with normal renal function. In children with renal disease, digoxin dosing must be carefully titrated based upon desired clinical response.

Long-term use of digoxin is indicated in many children who have been digitalized for acute heart failure, unless the cause is transient. Children with severe congenital heart disease, even after surgery, may require digoxin for prolonged periods.

It cannot be overemphasized that both the adult and pediatric dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.

HOW SUPPLIED

LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 50 μg (0.05 mg): bottles of 100. Imprint A2C (red)

LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 100 μg (0.10 mg)†: bottles of 100. Imprint B2C (yellow)

LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 200 μg (0.20 mg)†: bottles of 100. Imprint C2C (green)

†U.S. Patent No. 4088750

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CONTENTS

1014 Constrictive Pericarditis: New Aspects

NOBLE O. FOWLER

The current knowledge of constrictive pericarditis is reviewed briefly. Etiology, physical signs, electrocardiographic findings, hemodynamic features, and angiographic aspects are presented. Recent changes in etiology are discussed. The mechanism of the pericardial knock is elucidated. The fluid challenge procedure is described. The role and limitations of M-mode echocardiography in this disease are highlighted. The value of other noninvasive studies such as measurement of systolic time intervals, myocardial radioisotope scanning, and high-speed echocardiography is described. Emphasis is placed on the invasive and noninvasive methods that may be useful in separating restrictive cardiomyopathy from constrictive pericarditis. There is a brief commentary on the methods of treatment, indications for pericardial resection, and the current operative results.

1018 Echocardiographic Study of Right Ventricular Wall Motion in Cardiac Tamponade

PETER J. ENGEL, HENRY HON, NOBLE O. FOWLER, and SANDI PLUMMER

Twenty-one patients had M-mode echocardiographic recordings during cardiac tamponade. Seventeen of 21 had posterior motion of right ventricular endocardium at 0.05 second or longer after opening of the mitral valve. Sixteen of 17 patients with a large pericardial effusion without cardiac tamponade had posterior right ventricular wall motion that ceased at 0.05 second or less after opening of the mitral valve. The finding of early diastolic posterior motion of the right ventricular wall may signify diastolic collapse of the right ventricle and aids the echocardiographic identification of cardiac tamponade.

1022 Two-Dimensional Echocardiographic Findings in Cardiac Trauma

FLETCHER A. MILLER, Jr., JAMES B. SEWARD, BERNARD J. GERSH, ABDUL J. TAJIK, and PETER MUCHA, Jr.

Cardiac contusion is a potentially fatal complication of blunt chest trauma. The diagnosis is obscured because cardiac contusion usually occurs in a setting of multisystem trauma. Furthermore, the electrocardiographic changes are nonspecific. Experience with 2-dimensional echocardiography in evaluating cardiac trauma has not previously been emphasized. The results of 2-dimensional echocardiography are examined in 7 patients after significant blunt chest trauma. The findings show that 2-dimensional echocardiography is useful for diagnosing cardiac contusion, for estimating the extent of myocardial damage, and for identifying accompanying cardiac lesions such as thrombi, pericardial effusion, and valvular disruption.

1028 Assessment of Left Ventricular Relaxation in Patients With Valvular Regurgitation

MICHEL F. ROUSSEAU, HUBERT POULEUR, ANDRE A. CHARLIER, and LUCIEN A. BRASSEUR

The aim of the study was to assess ventricular relaxation in patients with mitral or aortic regurgitation. The hemodynamic and angiographic data were analyzed during the phase of decreasing left ventricular elastance (that is, when pressure is decreasing while volume is increasing) in 57 patients (27 with valvular regurgitation, 17 normal subjects, and 13 with coronary heart disease). Starting from a fixed level of wall stress (40 kdyne/cm^2), the incremental left ventricular elastance (ratio $\Delta P/\Delta V$) produced by a constant increase in left ventricular volume (+20 ml/m^2) was computed. In aortic and mitral regurgitation, the incremental elastance (−0.52 versus −0.95 mm Hg/ml/m^2 in normal subjects; $p < 0.001$) was abnormal. Significant correlations were found in the entire group between incremental elastance and ejection fraction ($r = 0.63$), and mean velocity of fiber shortening ($r = 0.62$), suggesting a relation between impaired incremental elastance and alterations in inotropic state or afterload, or both.

1037 Detection of Mild Aortic Regurgitation by Range-Gated Pulsed Doppler Echocardiography

RICARDO J. ESPER

To assess the sensitivity and specificity of the range-gated pulsed Doppler echocardiogram for the detection of aortic regurgitation, a study with use of this technique was carried out in 46 patients, classified into 3 groups: Group I was composed of 19 patients with a variety of heart diseases but with a competent aortic valve. Group II was composed of 17 patients who clinically and by auscultation had aortic regurgitation, confirmed by cardiac catheterization in 6. Group III was composed of 10 patients with aortic regurgitation but without the expected clinical or auscultatory evidence. Results show that the Doppler echocardiogram was more useful than ausculta-

Continued on Page A38

tion and echocardiography for the detection of mild aortic regurgitation. In this study the range-gated pulsed Doppler echocardiogram proved 100% sensitive and specific. However, it will be necessary to study larger groups in order to assess its utility in more complicated conditions (obesity, emphysema, and heart failure) and the differential diagnosis with other diastolic murmurs.

1044 Large V Waves in the Pulmonary Wedge Pressure Tracing in the Absence of Mitral Regurgitation

AUGUSTO D. PICHARD, RICHARD KAY, HARRY SMITH, PETER RENTROP, JAMES HOLT, and RICHARD GORLIN

The accurate diagnosis of mitral regurgitation has important therapeutic implications. Large V waves in the pulmonary wedge pressure may be misleading in the diagnosis of mitral regurgitation. Of 237 consecutive patients with high quality hemodynamic, angiographic, and echocardiographic data, 27 had large V waves (peak V 10 mm Hg greater than pulmonary wedge mean pressure). Ventriculograms were analyzed in blind fashion by 3 expert angiographers for any angiographic evidence of mitral regurgitation; 17 patients had mitral regurgitation (group I), and 10 did not (group II). The control group (group III) of 22 patients had normal V waves and no mitral regurgitation. Twenty-two hemodynamic and echocardiographic variables were compared among groups. It is concluded that large V waves in the pulmonary wedge pressure tracing can be seen in the absence of mitral regurgitation. The size of the V wave is related to factors that determine left atrial compliance. Caution is called for in the diagnosis of mitral regurgitation by pulmonary wedge pressure alone.

1051 Pregnancy in Patients With a Porcine Valve Bioprosthesis

UBERTO BORTOLOTTI, ALDO MILANO, ALLESSANDRO MAZZUCCO, CARLO VALFRE, ROSARIO RUSSO, MARIALUISA VALENTE, LUCIANO SCHIVAZAPPA, GAETANO THIENE, and VINCENZO GALLUCCI

Seven patients who became pregnant after valve replacement with a Hancock bioprothesis were followed up during 8 pregnancies. Six had undergone isolated mitral valve replacement, and 1 had mitral and aortic valve replacement. The only major complication during pregnancy was cardiac failure in 1 patient, associated with onset of atrial fibrillation. Results of this study show that (1) bioprosthetic valves can be considered the most suitable devices in women of childbearing age because anticoagulants can be avoided, therefore eliminating the risks related to inappropriate administration of oral anticoagulants as well as the hazards associated with the potential teratogenic effect of coumarin drugs; and (2) pregnancy might favor calcification of porcine heterografts, leading to bioprosthetic failure. Until further data are available to support this suspicion, close clinical and echocardiographic follow-up study of these patients is recommended after pregnancy.

ELECTROPHYSIOLOGIC STUDIES

1055 Electrophysiologic Drug Testing in Patients With Malignant Ventricular Arrhythmias: Importance of Stimulation at More Than 1 Ventricular Site

FRED MORADY, DAVID HESS, and MELVIN M. SCHEINMAN

Sixty-four patients with symptomatic ventricular tachycardia (VT) or ventricular fibrillation (VF) underwent right ventricular apical programmed stimulation and had no inducible VT during drug testing. Thirty patients (Group I) did not undergo left ventricular stimulation. Left ventricular stimulation in 38 drug trials induced no VT in 50% (Group IIA), nonsustained VT in 26% (Group IIB), and sustained VT in 24% (Group IIC). It is concluded that if only right ventricular apical stimulation is performed during electrophysiologic drug testing in patients with malignant ventricular arrhythmias, approximately 50% of drug trials may be incorrectly judged as suppressing the induction of VT. Drug therapy that suppresses VT induction with both right and left ventricular programmed stimulation results in a significantly better clinical response than therapy based on the results of only right ventricular stimulation.

1061 Electrophysiologic Study for Ventricular Arrhythmia: Effect on Total and Myocardial-Specific Creatine Kinase Activity

FRANCIS E. MARCHLINSKI, HARVEY L. WAXMAN, LESLIE M. SHAW, MARILYN D. EZRI, and MARK E. JOSEPHSON

After electrophysiologic study for ventricular arrhythmias, serially measured total creatine kinase enzyme activity was modestly elevated (greater than 2 X baseline or more than normal) at 24 hours in 10 (42%) of the 24 patients studied. However, no patient had an increase in creatine kinase B-subunit enzyme activity despite the need for emergency cardioversion in 9 of 14 patients with sustained ventricular tachycardia or fibrillation induced during electrophysiologic study and despite the presence of coronary heart disease in 14 (58%) of the 24 patients studied.

Continued on Page A40

the initial antihypertensive dosage of the beta blocker you prescribe...

	recommended initial dosa in hypertension
CORGARD[1] (Nadolol)	40 mg o.d.
TENORMIN[2] (Atenolol)	50 mg o.d.
LOPRESSOR[3] (Metoprolol Tartrate)	50 mg b.i.d.
INDERAL[4] (Propranolol Hydrochloride)	40 mg b.i.d.
BLOCADREN® (Timolol Maleate | MSD)	10 mg b.i.d.

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you prescribe

is

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nly BLOCADREN is resently indicated for the ost-MI patient to reduce e risk of reinfarction, and LOCADREN is the only eta blocker whose dosage as been established rough extensive clinical als to be the same for ost-MI as for initial therapy hypertension. In ypertension the starting osage is only 10 mg b.i.d. here is only one dosage for rophylactic use in stabilized atients surviving the acute hase of an MI: 10 mg b.i.d.

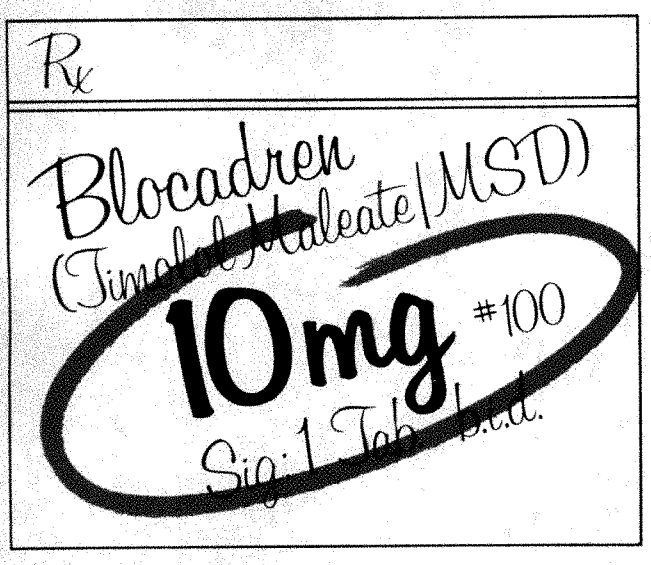
LOCADREN is contraindicated patients with: bronchospasm, cluding bronchial asthma, or vere chronic obstructive lmonary disease; sinus bradycardia; cond- and third-degree rioventricular block; overt cardiac lure (see below); cardiogenic ock; and hypersensitivity to

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, BLOCADREN should be

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal— Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

for initial therapy in hypertensive patients



Usual dosage range:
10 to 20 mg b.i.d.

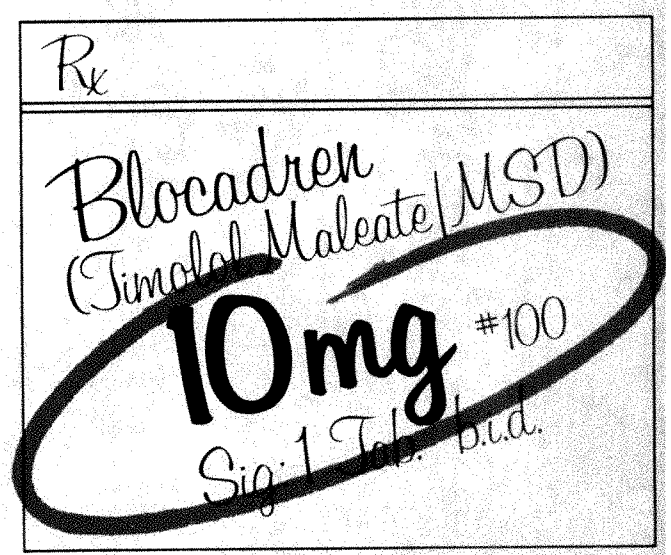
Maximum dosage:
30 mg b.i.d.

There should be an interval of at least seven days between increases in dosages.

Also available:
20-mg tablets

NOTE: IN HYPERTENSION
BLOCADREN may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

for reducing the risk of reinfarction in stabilized post-MI patients



Dosage:
10 mg b.i.d.

Treatment should be initiated within 1 to 4 weeks after infarction.

Data are not available as to whether benefit would ensue if initiated later.

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for initial therapy in hypertension and post-MI

For a Brief Summary of Prescribing Information, please see next page.

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CONTRAINDICATIONS:

Bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to this product.

WARNINGS:

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In Patients without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS:

General: Impaired Hepatic or Renal Function: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Dosing in the Presence of Marked Renal Failure: Marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20-mg doses. Dosing in such patients should therefore be especially cautious.

Drug Interactions: Close observation of the patient is recommended when BLOCADREN is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

Pregnancy—Category C: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n = 176) %	Placebo (n = 168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
INTEGUMENTARY		
pruritus	1.1	0
NERVOUS SYSTEM		
dizziness	2.3	1.2
vertigo	0.6	0
paresthesia	0.6	0
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta-blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction*		Withdrawal†	
	Timolol (n = 945) %	Placebo (n = 939) %	Timolol (n = 945) %	Placebo (n = 939) %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure—Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema—Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

*When an adverse reaction recurred in a patient, it is listed only once.

†Only principal reason for withdrawal in each patient is listed.

These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole*: extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular*: cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive*: gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Endocrine*: hyperglycemia, hypoglycemia; *Integumentary*: rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal*: arthralgia; *Nervous System*: local weakness; *Psychiatric*: depression, nightmares, somnolence, insomnia, nervousness, diminished concentration; *Respiratory*: cough; *Special Senses*: visual disturbances, dry eyes; *Urogenital*: impotence, urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System*: reversible mental depression progressing to catatonia; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular*: intensification of AV block (see CONTRAINDICATIONS); *Gastrointestinal*: mesenteric arterial thrombosis, ischemic colitis; *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Allergic*: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous*: reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

Clinical Laboratory Test Findings: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations.

1082 (DC7117610)

MSD MERCK SHARP & DOHME

For more detailed information, consult your MSD Representative and the Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

CONTENTS

1066 Amiodarone for Control of Sustained Ventricular Tachyarrhythmia: Clinical and Electrophysiologic Effects in 51 Patients

HARVEY L. WAXMAN, WILLIAM C. GROH, FRANCIS E. MARCHLINSKI, ALFRED E. BUXTON, LAURA M. SADOWSKI, LEONARD N. HOROWITZ, MARK E. JOSEPHSON, and JOHN A. KASTOR

The electrophysiologic effects of amiodarone and its ability to control ventricular arrhythmia were evaluated in a selected group of 51 patients with refractory sustained ventricular arrhythmia. Amiodarone prolonged refractoriness in the atria, atrioventricular (AV) node, and ventricle as well as conduction through the AV node and His-Purkinje system. Although it had no effect on sinus nodal recovery time and sinoatrial conduction time, it prolonged the sinus cycle length and 2 patients required a permanent pacemaker for symptomatic sinus bradycardia. Amiodarone did not alter the ease of VT inducibility in any consistent manner. Its clinical effectiveness could be evaluated in 46 patients. It provided effective therapy in 23, partly effective therapy in 13, and was ineffective in 10. Adverse effects were noted in 28 of 51 patients, and in 11 the drug had to be discontinued. It is concluded that amiodarone is useful for the treatment of refractory sustained ventricular arrhythmia, but its use should be reserved for patients with life-threatening sustained arrhythmia. Good clinical response can be observed in patients receiving amiodarone in spite of continued inducibility.

1075 Lack of Effectiveness of Oral Mexiletine in Patients With Drug-Refractory Paroxysmal Sustained Ventricular Tachycardia. A Study Utilizing Programmed Stimulation

EDWIN V. PALILEO, WILLIAM WELCH, JULIE HOFF, BORIS STRASBERG, ROBERT A. BAUERNFEIND, STEVEN SWIRYN, ALDO COELHO, and KENNETH M. ROSEN

Recent studies indicate that oral administration of mexiletine is useful in the therapy of recurrent ventricular tachycardia (VT). To further define the clinical usefulness of this drug, mexiletine was administered to 13 men and 4 women (mean age 62 years) who had drug-refractory paroxysmal sustained VT. All 17 patients had inducible sustained VT during the control electrophysiologic study and during serial electrophysiologic study on conventional drugs. The 47% incidence of noncardiovascular side effects was similar to that in previous reports, but the 29% incidence of arrhythmia potentiation by mexiletine was unexpectedly higher. Limited follow-up reveals recurrence of VT in 3 of 4 patients treated with oral mexiletine on a long-term basis. It is concluded that oral mexiletine does not appear useful in patients with drug-refractory, paroxysmal sustained VT. In addition, its use is associated with a high incidence of adverse effects, some of which can be serious and life-threatening.

1082 Prolongation of the Human Cardiac Monophasic Action Potential by Sotalol

DEBRA S. ECHT, LARRY E. BERTE, WILLIAM T. CLUSIN, ROLF G. SAMUELSSON, DONALD C. HARRISON, and JAY W. MASON

Sotalol and propranolol are nonselective, beta-blocking agents. Sotalol at a low concentration, unlike propranolol, prolongs the duration of the transmembrane action potential in vitro. In a double-blind study, we compared the electrophysiologic effects of intravenous sotalol (0.30 or 0.60 mg/kg; n = 9) with intravenous propranolol (0.15 or 0.20 mg/kg; n = 8) in 17 patients using bipolar suction electrodes in the right atrium and right ventricle to determine whether sotalol prolongs the monophasic action potential duration in man. After sotalol administration, there were significant increases in the Q-T interval, right atrial and right ventricular effective refractory periods, and right atrial and right ventricular monophasic action potential durations at 90% repolarization. Prolongation of the monophasic action potential duration was dependent on plasma sotalol concentration. There were no significant changes in these variables after propranolol. Sotalol, but not propranolol, acutely prolonged repolarization of human myocardium at a therapeutic plasma concentration. This property is unique among known competitive beta-adrenergic receptor antagonists.

1087 Use of Procainamide in Patients With the Wolff-Parkinson-White Syndrome to Disclose a Short Refractory Period of the Accessory Pathway

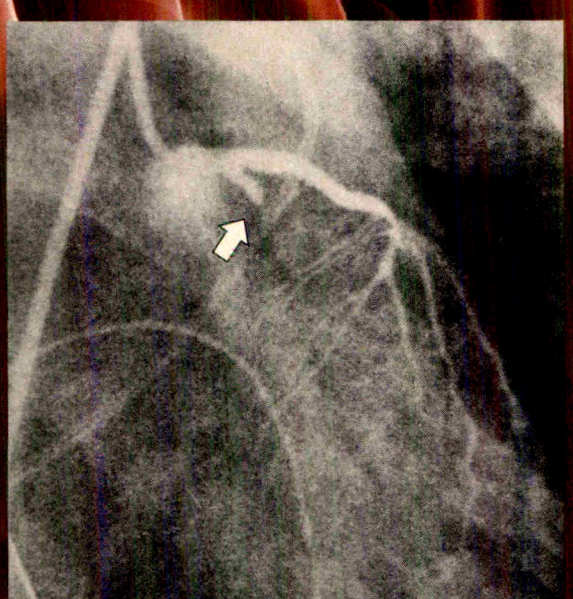
HEIN J. J. WELLENS, SIMON BRAAT, PEDRO BRUGADA, ANTON P. M. GORGELS, and FRITS W. BÄR

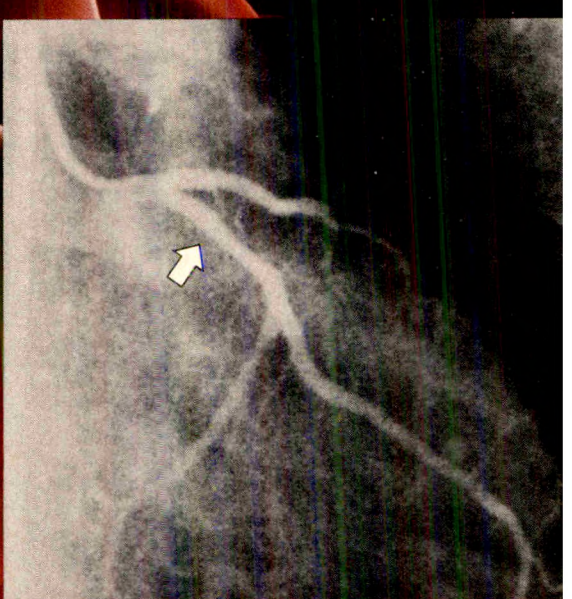
Procainamide administered intravenously (10 mg/kg body weight over 5 minutes) can be used to identify patients with the Wolff-Parkinson-White syndrome with a short anterograde refractory period of the accessory pathway. The development of complete anterograde block in the accessory pathway indicates that the patient has a re-

Continued on Page A47

In evolving transmural myocardial infarction

New therapy quickly dissolves acute coronary artery thrombi





Pre-streptokinase
A 38-year-old woman in cardiogenic shock with acute lateral wall myocardial infarction caused by complete left

Post-streptokinase
The left circumflex is now widely patent beyond previous site of obstruction (arrow).

Please see full prescribing information, a summary

STREPTASE®
(streptokinase)

now indicated for acute coronary artery thrombosis.

Streptase® is infused directly into the involved artery during cardiac catheterization.

Efficacy demonstrated in multicenter studies

Coronary artery reperfusion was accomplished in 174 of 221 patients (79%) during evolving transmural myocardial infarction.

Randomized, controlled studies are in progress to determine the effects of reperfusion on salvage of myocardial tissue and reduction of mortality.

Side effects: few and readily controlled

There were no reports of allergic reaction or fever. Seven cases of bleeding at the puncture site and one case of moderate peritoneal bleeding were controlled without terminating therapy. Severe bleeding was reported in only one patient. This patient had a gastric ulcer six months prior to treatment.

Prompt initiation of treatment critical

The greatest benefit is achieved when therapy is initiated within six hours after the onset of symptoms.

Thrombolytic activity and safety record well documented

Streptase® has been effectively used worldwide for nearly a decade. Its record of clinical success is well matched by its record of safety, and both have been extensively reported in the medical literature.

STREPTASE®
(streptokinase)

A major advance in M.I. therapy

Please see full prescribing information, a summary of which appears on the following page.

STREPTASE® (streptokinase)
Brief Summary
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

CORONARY ARTERY THROMBOSIS

Streptase® (streptokinase) has been reported to lyse acute thrombi obstructing coronary arteries, associated with evolving transmural myocardial infarction. Diagnosis of acute myocardial infarction has been confirmed, and the site of coronary thrombosis identified by selective coronary angiography. Other studies have demonstrated that (a) a thrombus is present in approximately 90% of patients evaluated within four hours of onset of symptoms; (b) when compared to concurrent or historical controls, the majority of patients who received intracoronary streptokinase within 6 hours of onset of symptoms showed a more immediate recanalization (within a few minutes vs hours/days) of the involved vessel.

IT HAS NOT BEEN ESTABLISHED THAT INTRACORONARY ADMINISTRATION OF STREPTOKINASE DURING EVOLVING TRANSMURAL MYOCARDIAL INFARCTION RESULTS IN SALVAGE OF MYOCARDIAL TISSUE, NOR THAT IT REDUCES MORTALITY. CONTROLLED STUDIES ADDRESSING THESE PARAMETERS ARE IN PROGRESS AND UNTIL COMPLETED, THOSE PATIENTS WHO MIGHT BENEFIT FROM THIS THERAPY CANNOT BE DEFINED.

CONTRAINDICATIONS

Because thrombolytic therapy increases the risk of bleeding, Streptase® (streptokinase) is contraindicated in the following situations:

- active internal bleeding
- recent (within 2 months) cerebrovascular accident, intracranial or intraspinal surgery (see WARNINGS)
- intracranial neoplasm

WARNINGS

Bleeding

The aim of Streptase® (streptokinase) therapy is the production of sufficient amounts of plasmin for the lysis of intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example, at sites of needle punctures, are also lysed and bleeding from such sites may occur.

Intramuscular injections and nonessential handling of the patient must be avoided during treatment with Streptase® (streptokinase). Venipunctures should be performed carefully and as infrequently as possible.

Should an arterial puncture be necessary during intravenous therapy, upper extremity vessels are preferable. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

When internal bleeding occurs, it may be more difficult to manage than that which occurs with conventional anticoagulant therapy.

In the following conditions the risks of therapy may be increased and should be weighed against the anticipated benefits.

- Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels
- Recent serious gastrointestinal bleeding (within 10 days)
- Recent trauma including cardiopulmonary resuscitation
- Severe, uncontrolled arterial hypertension
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Subacute bacterial endocarditis
- Hemostatic defects including those secondary to severe hepatic or renal disease
- Pregnancy
- Cerebrovascular disease
- Diabetic hemorrhagic retinopathy
- Prior severe allergic reaction to streptokinase
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Should serious spontaneous bleeding (not controllable by local pressure) occur, the infusion of Streptase® (streptokinase) should be terminated immediately and treatment instituted as described under ADVERSE REACTIONS.

Use of Anticoagulants

Concurrent use of anticoagulants with intravenous administration of Streptase® (streptokinase) is not recommended. However, concurrent use of heparin may be required during intracoronary administration of Streptase® (streptokinase). Clinical studies with concurrent use of heparin and lower Streptase® (streptokinase) dosages employed during intracoronary administration have demonstrated no tendency toward increased bleeding that would not be attributable to the procedure or Streptase® (streptokinase) alone. Nevertheless, careful monitoring for excessive bleeding is advised.

Arrhythmias

Rapid lysis of coronary thrombi has been reported occasionally to cause reperfusion atrial or ventricular dysrhythmias requiring immediate treatment. During studies, careful monitoring for arrhythmia was maintained during and immediately following intracoronary administration of Streptase® (streptokinase).

PRECAUTIONS

Use in Pregnancy and Children

Safety and effectiveness of Streptase® (streptokinase) therapy in children and during pregnancy have not been established. Therefore, treatment of such patients is not recommended.

Drug Interactions

The interaction of Streptase® (streptokinase) with other drugs has not been studied. Drugs that alter platelet function should not be used during therapy. Common examples are: aspirin, indomethacin, and phenylbutazone.

Patient Monitoring

Before commencing thrombolytic therapy, it is desirable to obtain a thrombin time (TT), activated partial thromboplastin time (APTT), prothrombin time (PT), hematocrit and platelet count to obtain hemostatic status of the patient.

Intracoronary Artery Infusion

During studies, laboratory monitoring of hemostatic parameters during intracoronary artery infusion showed minimal changes, if any. Heparin was continued during therapy or instituted following therapy and monitored accordingly.

ADVERSE REACTIONS

The following adverse reactions have been frequently associated with intravenous therapy but may also occur with intracoronary artery infusion:

Bleeding

Minor bleeding occurs often with thrombolytic therapy mainly at invaded or disturbed sites. When lytic therapy is continued while local measures are used to control minor bleeding, do **not** reduce the dose as this will increase lytic activity since more plasminogen will be available for conversion to plasmin. Severe internal bleeding involving gastrointestinal, genitourinary, retroperitoneal or intracerebral sites, may occur. Several fatalities due to cerebral and other serious internal hemorrhage have occurred during intravenous thrombolytic therapy.

Should uncontrollable bleeding occur, Streptase® (streptokinase) infusion should be discontinued and, if necessary, blood loss and reversal of the bleeding tendency can be effectively managed with whole blood (fresh blood preferable), packed red blood cells and cryoprecipitate or fresh frozen plasma. Although the use of aminocaproic acid (ACA, AMICAR®) in humans as an antidote for streptokinase has not been documented, it may be considered in an emergency situation.

Allergic Reactions

Reactions attributed to possible anaphylaxis have been observed rarely in patients treated with Streptase® (streptokinase) intravenously. These ranged in severity from minor breathing difficulty to bronchospasm, periorbital swelling or angioneurotic edema. Other milder allergic effects such as urticaria, itching, flushing, nausea, headache and musculoskeletal pain have also been observed.

Mild or moderate reactions may be managed with concomitant antihistamine and/or corticosteroid therapy. Severe allergic reactions require immediate discontinuation of Streptase® (streptokinase), with adrenergics, antihistamines, or corticosteroids administered intravenously as required.

Fever

Although Streptase® (streptokinase) is nonpyrogenic in standard animal tests, approximately one-third of patients treated with Streptase® (streptokinase) intravenously have shown increases in body temperature of ≥ 1.5°F. Symptomatic treatment is usually sufficient to alleviate discomfort. The use of acetaminophen rather than aspirin is recommended.

DOSAGE AND ADMINISTRATION

Lysis of Coronary Artery Thrombi

During clinical studies, Streptase® (streptokinase) was administered selectively into the thrombosed coronary artery via coronary catheter placed by the Judkins or Sones Technique. When administered within 6 hours of onset of symptoms of acute transmural myocardial infarction, at a bolus dose averaging 20,000 IU and a maintenance dose averaging 2,000 IU/min for 60 minutes, greater than 75% of occlusions were opened in less than 1 hour.

How Supplied

Streptase® (streptokinase) is supplied as a lyophilized white powder in 6.5 mL vials (in packages of 10) with color-coded labels corresponding to the amount of purified Streptase® (streptokinase) in each vial as follows:

green — 250,000 IU blue — 750,000 IU

Store unopened vials at controlled room temperature (15-30°C).

Distributed by: **Hoechst-Roussel** Pharmaceuticals Incorporated Somerville, New Jersey 08876 **Hoechst**

Manufactured by: Behringwerke AG U.S. License #97

Q7044-6

fractory period of the accessory pathway 270 ms or longer. If preexcitation persists the patient has a short anterograde refractory period of the accessory pathway. The use of procainamide administered intravenously is a reliable and rapid method for identifying patients with the Wolff-Parkinson-White syndrome possibly at risk for circulatory insufficiency or sudden death in case of atrial fibrillation.

1090 Electrophysiologic Effects of Flecainide Acetate in Patients With Sinus Nodal Dysfunction

HARALD VIK-MO, OLE-JØRGEN OHM, and PER LUND-JOHANSEN

Flecainide acetate is a new antiarrhythmic agent with class I properties and a long plasma half-life for oral and intravenous use. The electrophysiologic effects of 1.5 mg/kg administered intravenously were evaluated in 11 patients with sinus nodal dysfunction. Flecainide acetate increased the corrected sinus node recovery time by 97%, whereas sinus cycle length and sinoatrial conduction time were not significantly changed. Flecainide acetate markedly prolonged the atrial and ventricular conduction and refractoriness, and thus appears to be a potent antiarrhythmic agent. However, sinus nodal function is depressed by flecainide acetate and caution is advised in the use of flecainide acetate in patients with sinus nodal dysfunction.

1095 Epicardial Activation of the Human Ventricle: Effects of Left Ventricular Hypertrophy

ISAAC WEINER, BRUCE MINDICH, and ROBERTA PITCHON

Epicardial mapping was performed in 10 patients with left ventricular hypertrophy. Nine patients had a single epicardial breakthrough site on the anterior right ventricle; 1 patient had a right ventricular breakthrough and a single left ventricular breakthrough. Nine patients had latest epicardial breakthrough at the left ventricular base and 1 patient had latest activation at the right base. Compared with patients without hypertrophy, patients with left ventricular hypertrophy had fewer left ventricular breakthrough points and were more likely to have latest activation at the left ventricular base. Thus, left ventricular hypertrophy is associated with marked changes in the pattern of epicardial activation.

1099 Influence of the Autonomic Nervous System on the Q-T Interval in Man

KEVIN F. BROWNE, DOUGLAS P. ZIPES, JAMES J. HEGER, and ERIC N. PRYSTOWSKY

Drugs that affect the autonomic nervous system can influence the Q-T interval directly or by changing the rate. Bazett's formula to correct for rate may be misleading after certain drug interventions. We tested this hypothesis in 20 patients receiving both propranolol and atropine. Sinus cycle length, measured Q-T interval (QT_m), atrially paced Q-T interval (QT_p), and the ventricular effective refractory period shortened after atropine plus propranolol ($p < 0.001$), but the corrected Q-T interval (QT_c) using Bazett's formula did not change. The sinus cycle length increased after propranolol but no change occurred in $Q\text{-}T_m$ or QT_p, although $Q\text{-}T_c$ markedly shortened ($p < 0.001$). Sinus cycle length, $Q\text{-}T_m$, and $Q\text{-}T_p$ decreased after atropine ($p < 0.01$) but $Q\text{-}T_c$ lengthened ($p < 0.01$). In summary, atropine and atropine plus propranolol shorten the Q-T interval independent of rate, demonstrating a direct vagal effect on the Q-T interval. Bazett's formula inaccurately predicts the Q-T interval after administration of atropine, propranolol, and atropine plus propranolol.

1104 Subcostal M-Mode Echocardiography of the Right Atrial Wall in the Diagnosis of Cardiac Arrhythmias

NIKSA DRINKOVIC

M-mode echocardiography of the right atrial (RA) wall can be easily recorded from the subcostal location. In a normal RA wall motion pattern, atrial contraction is represented by a markedly prominent posterior motion. The presence or absence of atrial contractions in the subcostal RA wall echocardiogram, their amplitude, and their timing may help in the diagnosis of cardiac arrhythmias with the simultaneously recorded electrocardiogram. Flat and hidden P waves can be accurately identified. It is possible to distinguish between atrial, ventricular, and nodal premature beats and to recognize atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia, paroxysmal atrial tachycardia with block, atrioventricular (AV) nodal tachycardia, and supraventricular tachycardia with aberrant conduction. The diagnosis of wandering pacemaker, AV dissociation, sinoatrial block, and AV block is facilitated. On the basis of a study of 60 patients with various rhythm disturbances, it was concluded that analysis of the subcostal RA wall echocardiogram is a new, helpful noninvasive approach in the diagnosis of cardiac arrhythmias.

Continued on Page A55

2D Echocardiography

PNT # C-18623
R. DREXTER
DATE 09/30/82
R/O ANTERO-SEPTAL
INFRACTION

PATIENT RI
ST. FRANC

HT: 162.56 cm WT: 61 kg AGE: 60 Yrs BSA 1.652m2 HR: 96.BPM BP: 144/ 72 (s/

MEASUREMENTS

LV DIAMETER (LAX)			NORMALS
Diastolic	4.835	cm	(3.6-5.2)
Systolic	3.232	cm	(2.3-3.9)
Fractional Shtng	.331		(.18-.42)
IVS THICKNESS			NORMALS
Diastolic	1.037	cm	(0.6-1.1)
Systolic	1.215	cm	
Fractional Change	.172		
LVPW THICKNESS			NORMALS
Diastolic	1.138	cm	(0.6-1.1)
Systolic	1.276	cm	
Fractional Change	.122		
Dias IVS/LVPW	.911		
SAX AREA			NORMALS
Diastolic	15.506	cm2	(9.5-22.3)
Systolic	10.706	cm2	(4.0-11.6)
Fractional Change	.31		(.36-.64)
LV LENGTH			NORMALS
Diastolic	7.472	cm	
Systolic	7.234	cm	
Fractional Shtng	.032		
LA DIAMETER			NORMALS
Systolic	3.76	cm	(2.1-3.7)
MITRAL VALVE			NORMALS
Area	4.219	cm2	

DERIVED FORMULAS

Views: (SAX+LAX+4CV)

EJECT. FRAC FROM FS			NORI
EF (estimated)	.348		
EF (measured)	.336		
BULLET FORMULA			NORI
Ejection Fraction	.332		
Diastolic Vol	96.55	ml	
Systolic Vol	64.541	ml	
Stroke Volume	32.009	ml	
Cardiac Output	3.084	l/min	
SIMPSONS RULE FORMULA			NORI
Ejection Fraction	.34		
Diastolic Vol	99.156	ml	
Systolic Vol	65.422	ml	
Stroke Volume	33.734	ml	
Cardiac Output	3.25	l/min	
ELLIPSOID FORMULA			NORI
Ejection Fraction	.337		
Diastolic Vol	103.106	ml	
Systolic Vol	68.346	ml	
Stroke Volume	34.76	ml	
Cardiac Output	3.349	l/min	

COMMENTS AND RECOMMENDATIONS:

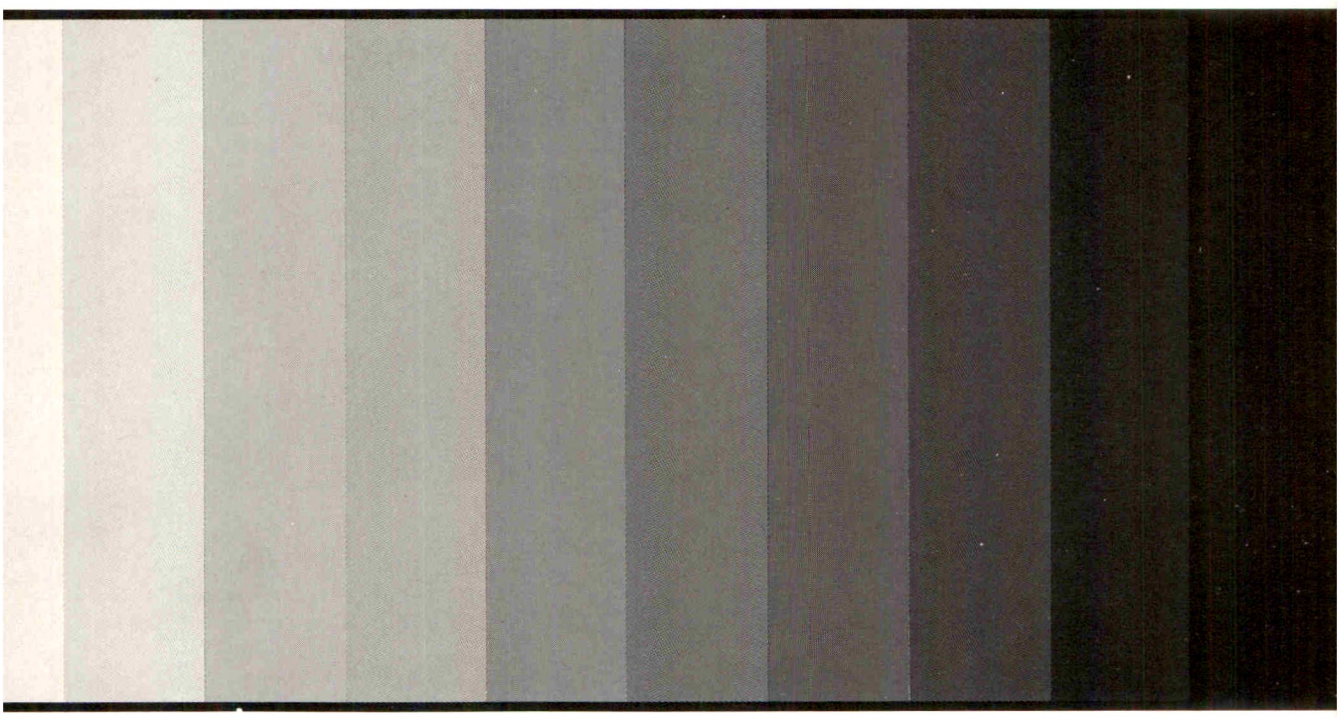
Values normal
Basilar ventricular wall motion, Hyperkynesis at base of septum
Hypokynesis of posterior and lateral walls
Apex exam - Dyskynesis of the distal septum and akynesis of the lateral walls

Final Impression: Marked wall motion abnormalities; the only area appearing to move well being the Basilar anterior and septal wall.

B. Oliver, M.D.

MICRO SONICS, 1050 E. 49TH STREET, INDIANAPOLIS, IN 46205 (317) 283-2222 TELEX: 27-62

Methods for Clinical Measurements and Quantification of Two-Dimensional Echocardiography



Presented by

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Indianapolis, IN 46205
(317) 283-2222
Telex: 27-6210

From What Views and Where Should Measurements be Made

Mitral valve orifice size is assessed in the parasternal short axis view. Although 2DE provides multiple views for the measurement of the other variables mentioned, the parasternal long axis view presents several advantages for quantitation. The first is a perspective which is similar to that seen in M-Mode, with the distinct advantage of reliance primarily on axial resolution of the ultrasonic beam. Visualization of structures perpendicular to the direction of the ultrasonic beam is clearly superior to the resolution of structures which are parallel to the beam. In the parasternal long axis view, the interventricular septum, posterior left ventricular wall, and anterior and posterior walls of the left atrium are essentially perpendicular to the ultrasonic beam.

End-diastole is generally defined by the peak of the R wave as noted on simultaneous ECG tracings. Images which do not include an ECG tracing can use the frame showing the largest size attained by the left ventricular cavity, generally occurring right after the mitral valve A wave. End-systole is more accurately defined by mechanical events, inasmuch as Q-T interval changes may result in inconsistent relationships between the T wave and mechanical systole. End-systole is found by noting the smallest left ventricular cavity size and should occur just prior to the opening of the mitral valve.

The American Society of Echocardiography recommends that M-Mode measurements be made by use of the leading edge method.[3] That is, measurements from one structure to another should be made from the leading edge of the last echo produced by the anterior structure to the leading edge of the first echo produced by the posterior structure. Though preliminary work regarding this aspect of 2DE quantitation has been done, confirmation of this method is still incomplete. Technically it is often difficult to measure from the leading edge of several structures, particularly the left ventricular side of the septum. While appreciating this, measurements should probably be made as close to the leading edge method as feasible. All measurements in this paper were made using the leading edge method (as perceived in real-time) whenever possible.

Measurements of the Left Ventricle

Diameter measurements of the left ventricular cavity are made from a point on the posterior wall endocardium, at the level at which the chordae tendineae attach to the papillary muscle, to a point on the left side of the interventricular septum, such that a line connecting the two points is perpendicular to the long axis of the left ventricle (see Figs. 1 and 2). This measurement is made in end-systole and end-diastole. From these measurements, fractional shortening is obtained by the formula: diastolic diameter minus systolic diameter divided by diastolic diameter $\left(\frac{LVd-LVs}{LVd}\right)$. Though probably useful in diseased states which affect global left ventricular function uniformly, it must be appreciated that this simple fractional shortening formula is markedly limited in any state which causes wall motion abnormalities which are localized. Fractional shortening in the patient who has abnormalities of the interventricular septum or posterior wall at the level at which measurements have been made may have falsely depressed values suggesting left ventricular function is poorer than it actually is. Conversely, wall motion abnormalities of the lateral wall and apex wall may not be reflected by fractional shortening.

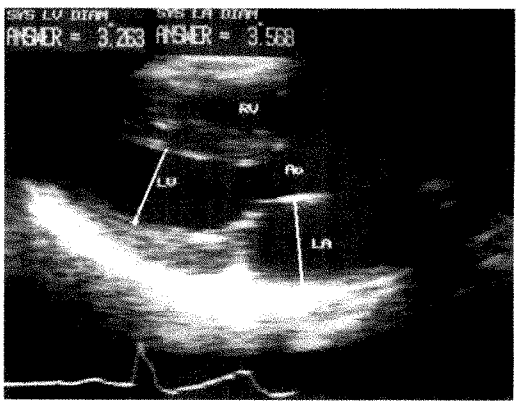


Fig. 1: Parasternal Long Axis Systole

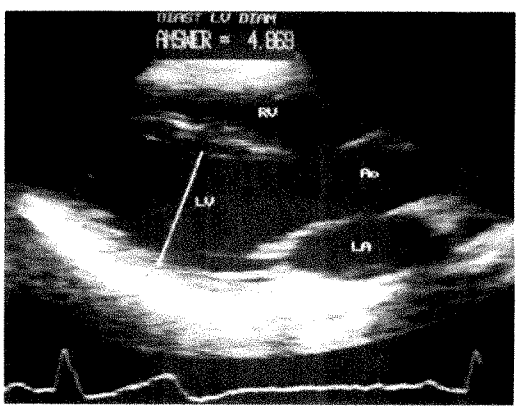


Fig. 2: Parasternal Long Axis Diastole

Several pitfalls in measuring dimensions of the left ventricular cavity should be noted. First and most importantly, measurements must be made from high quality echocardiograms; endocardial definition must be clear. Not infrequently, echos which provide valuable subjective information are simply inadequate for quantitation. Secondly, efforts must be made to insure that the measurement being made is a true maximal diameter of the left ventricle. Though theoretically more likely to provide this measurement than M-Mode echocardiography, 2DE too can provide misleading information if the parasternal long axis view is not taken through a true sagittal plane. Clues to suggest that the plane of the parasternal long axis is not proper include a distorted shape of the left ventricular cavity, marked variation in cavity size not related to contraction, and the appearance of a 'pseudo-apex'. Parasternal long axis views of the left ventricle which show an apparent apex are often out of the sagittal plane of the left ventricle such that this pseudo apex is probably formed by lateral or medial walls rather than the true LV apex. This results in a left ventricular diameter value which is smaller than that seen with a proper view.

Wall Thickness

Measurement of the thickness of the interventricular septum and posterior left ventricular wall are made in end-diastole. The level at which these measurements are made is dependent upon adequate visualization of endocardium and epicardium. Measurements are generally made between the papillary muscle and the mitral valve on the posterior left ventricular wall (see Fig. 3). Caution must be made to identify the papillary muscle so that this will not be included in assessment of wall thickness.

Methods for Clinical Measurements and Quantification of Two-Dimensional Echocardiography

Summary

The purpose of this protocol is to acquaint the reader with rationale and methods for quantitation of two dimensional echocardiographic images. Reasons for the theoretical advantages of these methods over M-Mode are given. Specific techniques for measurements of various parameters are described in detail and their utility is discussed. Finally, newer preliminary work in quantitative two dimensional echocardiography is described with reflection on its potential uses.

Quantitative Two Dimensional Echocardiography: An Overview

Why Quantitative Two Dimensional Echocardiography

Echocardiography (echo) has provided an invaluable tool in the non-invasive assessment of patients with cardiac disease. Qualitative assessment of echo patterns provide diagnoses in a large number of clinical entities. M-Mode echo has demonstrated particular usefulness when used quantitatively. Over the years, relatively simple M-Mode echo measurements have tremendously benefited the clinician by offering objective data for comparison with established values and for sequential comparison in the individual patient.

Though still in its infancy, quantitative two dimensional echocardiography (2DE) offers a number of potential benefits over M-Mode. Limited echo windows often provide M-Mode views which do not truly define the plane of interest. Variations in echocardiographic windows, chest configuration, heart shape, and heart size from patient to patient can result in markedly different planes of the left ventricle being defined as the maximum diameter by M-Mode. The problem of locating the true left ventricular diameter perpendicular to its long axis is partially solved by the improved visual presentation of 2DE. Similar problems involving the proper location of other M-Mode measurements are also partially solved by the use of 2DE.

Methods of Measurement

Just as the development of hard-copy M-Mode presented an opportunity for convenient quantitation of images, recent advances have made quantitative 2DE more attractive. Preliminary measurements of 2DE examinations had to be made directly from the viewing screen using calipers and grid markings or by a similar technique using Polaroid photographs. Recently, improved video tape recorders have made possible sharper images which are more suitable for measurements.

The Micro Sonics Image Analysis Computer is used to review patient studies archived on video tape as well as to make measurements. Segments of the video taped patient study are transferred to Video Disk allowing single frame or cine viewing in forward or reverse directions. Measurements are then made directly on the video screen with on-screen joy-stick controlled electronic calipers. Those measurements can then be combined in a variety of pre-entered formulas. A digitizing tablet could also be used to enter data from hard-copy.

Clinically Useful Two Dimensional Echocardiographic Measurements

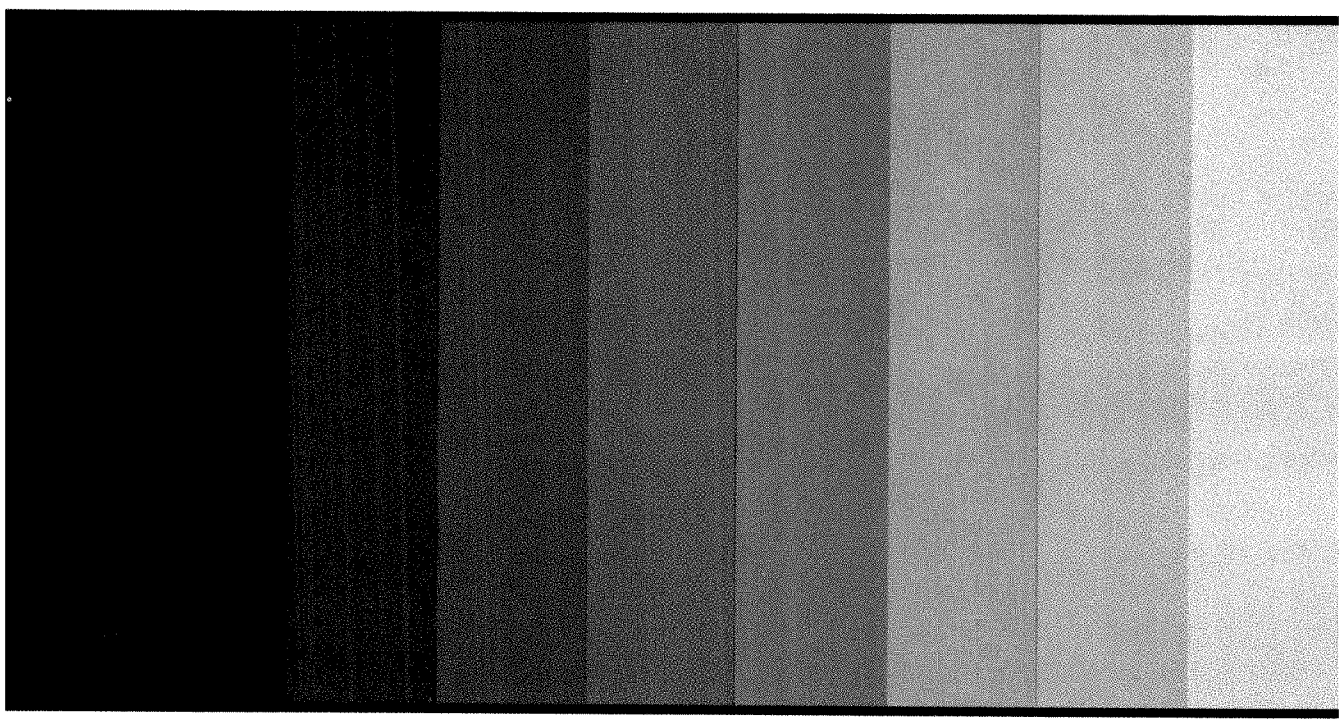
Whose Echocardiogram Needs Measurement

All patients do not require extensive quantitation of their echocardiogram. Patients in whom measurements are particularly useful fall into two general categories. The first category is the patient whose quantitative values add to the overall assessment of the echocardiogram. This group includes those in which subjective assessment suggests that measurements might be abnormal, for instance, left ventricular hypertrophy or dilation of the left ventricle or atrium. The second category includes patients whose measurements might initially be normal, but for whom sequential studies are anticipated.

What Structures Should be Measured

Until well established criteria for 2DE measurements become widely accepted, it is probably prudent to rely primarily on measurements which are an extension of recognized M-Mode techniques. Preliminary data suggests that values from 2D images for diastolic and systolic left ventricular diameter, systolic left atrial diameter, fractional shortening of the left ventricle, and left ventricular posterior and septal wall thicknesses are similar to those seen with M-Mode. In addition, published data documents the usefulness of 2DE measurement of mitral valve area in patients with rheumatic mitral stenosis.[1,2]

Methods for Clinical Measurements and Quantification of Two-Dimensional Echocardiography



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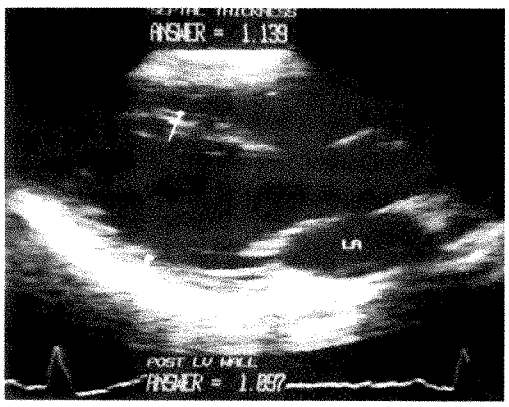

Fig. 3: Parasternal Long Axis Diastole

The Left Atrium

Assessment of the left atrial diameter is done in end-systole. This relatively simple measurement is made from a point on the posterior aortic root to the posterior wall of the left atrium (see Fig. 1). 'Side lobe' artifacts, which can be troublesome in M-Mode echo when making this measurement, are generally more easily identified with 2DE. Occasionally, the descending aorta or a large coronary sinus can be visualized posterior to the left atrial wall; these structures must be distinguished in relation to the atrium.

Rheumatic Mitral Stenosis

Planimetry of the mitral valve orifice in patients with rheumatic mitral stenosis is accomplished by use of the parasternal short axis view (Fig. 4). Care must be taken to assess the mitral valve at the level

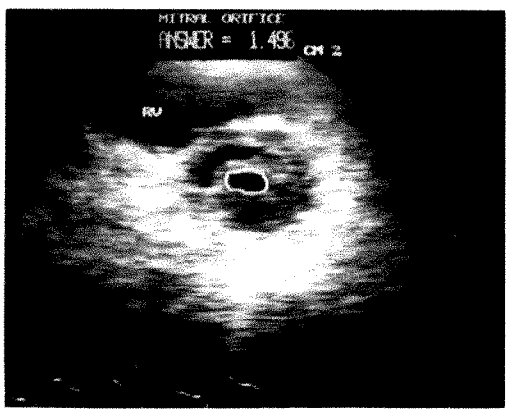

Fig. 4: Parasternal Short Axis Systole at Tips of Mitral Leaflets

of its leaflet tips. This is accomplished by obtaining recordings which slowly scan the body of the mitral valve apically toward the chordae tendineae. By use of this technique, both the technician and the person interpreting the echocardiogram can be relatively certain that the area being analyzed is in fact representative of the mitral valve orifice at its tips. Failure to insure that the area being planimetered is proper will result in computations which are falsely high, representing a measurement of the body of the mitral valve and not its true orifice. After locating the proper level, the image is slowly played until it demonstrates the largest mitral valve orifice size seen in early diastole. This area is then planimetered by utilizing computer assisted area assessment.

Other Chambers

Although most clinical echocardiographic laboratories make use of M-Mode quantitation of the right ventricular dimension, visualization with 2DE presents an image which is more confusing to measure than the left ventricle or left atrium. The unusual shape of the right ventricle as appreciated by 2DE, presents questions as to where measurements should be made. Assessment of this chamber and of the right atrium by 2DE will likely be a valuable contribution of the technique; however, this awaits further study.

Potentially Useful Two Dimensional Echocardiographic Measurements not Appreciated in M-Mode

Preliminary information both published and unpublished has suggested a great potential for measurements which are not possible using the M-Mode technique alone. In addition to linear measurements, area measurements of the left ventricle particularly in the parasternal short axis view, can easily be made with the Micro Sonics computer. By measuring this area at a particular level, for instance at the papillary muscles (see Figs. 5, 6), and by use of a similar formula as used for fractional shortening, fractional area change can be calculated (Fig. 7): Diastolic Area minus Systolic Area divided by Diastolic Area ($\frac{DA-SA}{DA}$). This value may theoretically provide more information regarding ventricular function than single plane fractional shortening.

Volumetric data from the left ventricle and other chambers has been obtained using a wide variety of geometric assumptions.[4] Planimetry of the area of the left ventricle in apical views has been used to calculate volumes in much the same way as is done using right anterior oblique angiograms.[5] Kennedy and Dodge formulas, as well as modified Simpson's Rule formulas, can be utilized with this

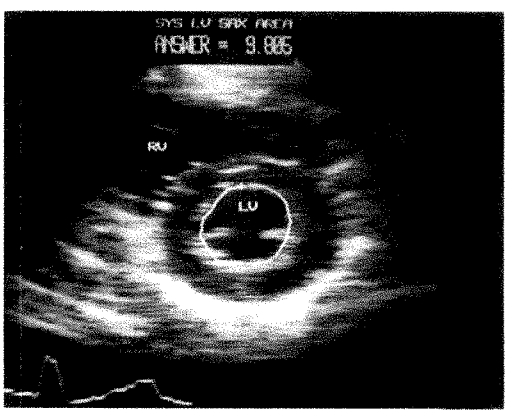

Fig. 5: Parasternal Short Axis Systole Papillary Level

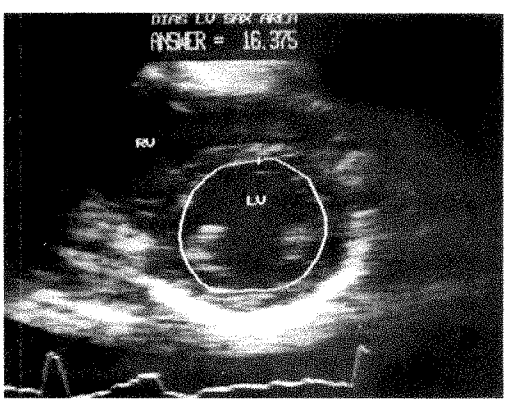

Fig. 6: Parasternal Short Axis Diastole Papillary Level

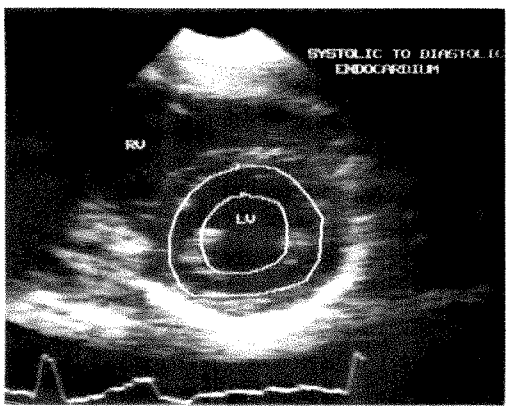

Fig. 7: Parasternal Short Axis Comparison Systole and Diastole.

technique. More complex Simpson's Rule formulas employ multiple views of the left ventricle and usually require computer assistance.[6,7] One rather simple geometric assumption which has shown fair correlation in some studies is the "Bullet" or cylinder-ellipse model where volume is equal to 5/6 times short axis area times the length of the left ventricle (LVVolume = 5/6AL).[4,8] This calculation can be made from the short axis measurement described previously and a left ventricular length measurement made from an apical view.

Assessment of ejection fraction has been made by some investigators by use of volumetric data obtained by the various geometric assumptions. More recently, at least one technique has been proposed which provides a calculation of ejection fraction by assessment of diastolic and systolic diameters in multiple views at various levels.[9]

Conclusion

Quantitative echocardiography provides relatively inexpensive non-invasive data for comparison with established values and for comparison with previous examinations on the same patient. Two dimensional echocardiography has several theoretical advantages over M-Mode for quantitation. Until more extensive 2DE quantitative information is available, measurements which are an extension of the M-Mode technique can reliably be used. Preliminary reports suggest that volumetric and ejection fraction data can be obtained utilizing two dimensional echocardiography; these techniques may come into general clinical use in the near future.

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We gratefully acknowledge and thank the people of the Echocardiography Laboratory at Indiana University School of Medicine for their assistance in the preparation of this material.

METHODS

1109 Application of Body Surface Mapping to Exercise Testing: S-T_{80} Isoarea Maps in Patients With Coronary Artery Disease

FRANK G. YANOWITZ, G. MICHAEL VINCENT, ROBERT L. LUX, MAHESH MERCHANT, LARRY S. GREEN, and J. A. ABILDSKOV

Body surface electrocardiographic maps were obtained during exercise testing in 25 men with coronary artery disease. Torso potential distributions at 192 locations were derived from a 32 lead electrode array. The S-T segment was characterized by the spatial distribution of an 80 ms S-T segment integral. Body surface regions where the S-T_{80} areas were −8 mv·ms or greater were identified in 18 of 25 patients. The most negative site on the isoarea maps was called the "S-T_{80} minimum." The S-T_{80} minima were located 1 or 2 electrode rows away from the standard V_4–V_6 electrode positions in 6 of 18 patients. The data suggest that the standard electrocardiographic leads may not be optimal for identifying S-T segment depression in all patients with coronary disease. Furthermore, body surface mapping during exercise provides a more quantitative and qualitative method for examining the ischemic response to exercise.

1114 Scintigraphic Prediction of Pulmonary Arterial Systolic Pressure by Regional Right Ventricular Ejection Fraction During the Second Half of Systole

BRUCE J. FRIEDMAN and B. LEONARD HOLMAN

In 49 patients who had undergone gated equilibrium ventriculography and cardiac catheterization within a several-day interval, total and fractional portions of global and regional right ventricular ejection fraction were correlated with pulmonary arterial systolic pressure. The fractional ejection of blood from the region of the right ventricular free wall during the second half of systole as measured by gated equilibrium scintigraphy accurately detected pulmonary hypertension. Although a good correlation between pulmonary arterial systolic pressure and regional right ventricular ejection during the second half of systole was found, small changes in ejection fraction reflect large changes in pressure in the abnormal range, limiting the technique's application as a quantitative index of pulmonary arterial pressure.

1120 Effect of Beam Directional Alterations on Left Ventricular Shortening Fraction

HEINZ R. HOENECKE, Jr., STANLEY J. GOLDBERG, DAVID J. SAHN, HUGH D. ALLEN, and LILLIAM M. VALDES-CRUZ

The effect of ultrasonic beam direction on echocardiographically determined shortening fraction of the left ventricle was examined. This was accomplished by studying results of several M-mode lines at the chordal level from a single 2-dimensional image. The results demonstrate that many M-mode lines that deviate from the meridian of the ventricle may provide acceptable M-mode tracings but considerably different results for shortening fraction. Accordingly, if shortening fraction is to be used clinically, spatial orientation is recommended.

1124 Low Energy Countershock Using an Intravascular Catheter in an Acute Cardiac Care Setting

RAYMOND YEE, DOUGLAS P. ZIPES, SAJAD GULAMHUSEIN, MICHAEL J. KALLOK, and GEORGE J. KLEIN

A tripolar countershock catheter was inserted into 8 patients for purposes of cardioversion and defibrillation of refractory ventricular tachyarrhythmias. The catheter was inserted percutaneously through the left subclavian vein with the distal tip in the right ventricular apex, and direct current countershock was delivered using a standard commercially available defibrillation unit. No complications or lead dislodgment occurred after a total of 45 patient-days with the catheter in situ. Six patients required catheter countershock for 91 episodes of ventricular tachycardia, 3 of ventricular flutter, and 6 of ventricular fibrillation. Catheter countershock was delivered 115 times and was successful on 93 occasions (80%), using energy doses of 2.5 to 40 J. Burst pacing to terminate ventricular tachycardia was performed successfully 10 times in 1 patient. Thus, catheter countershock can be safely and effectively administered in an acute care setting and is an alternative to repeated transthoracic countershock for termination of unstable refractory ventricular tachyarrhythmias.

1130 Intraoperative 2-Dimensional Echocardiography: Ejection of Microbubbles From the Left Ventricle After Cardiac Surgery

PAUL C. RODIGAS, FRANCES J. MEYER, GEORGE B. HAASLER, JEROME M. DUBROFF, and HENRY M. SPOTNITZ

The prevalence of ejection of microbubbles from the left ventricle after open-heart surgery was studied with intraoperative 2-dimensional echocardiography using a gas-sterilized transducer. High-quality images of the left atrium, left ventricle, and ascending aorta were obtained and demonstrated microbubbles as bright echo reflec-

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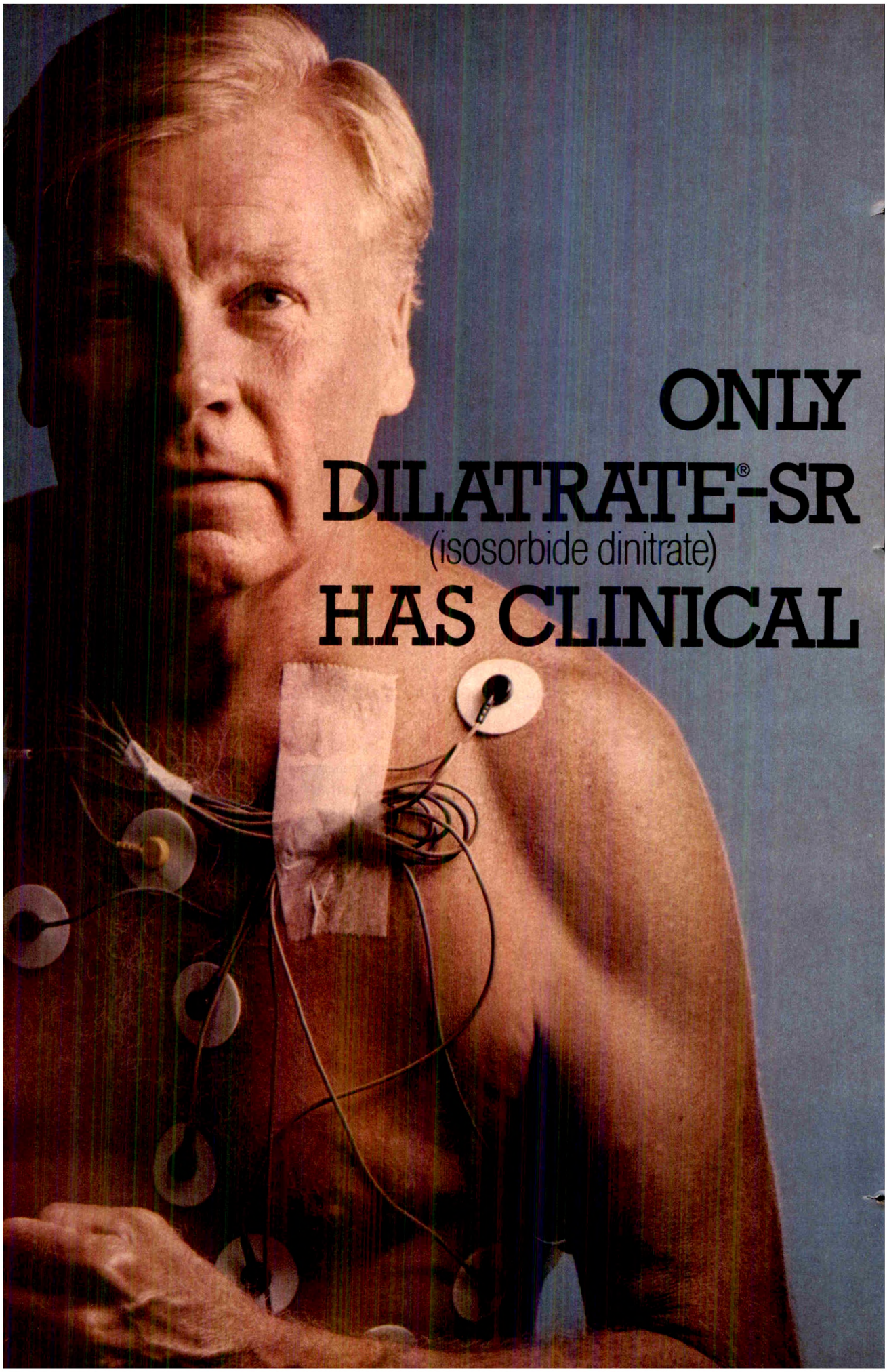
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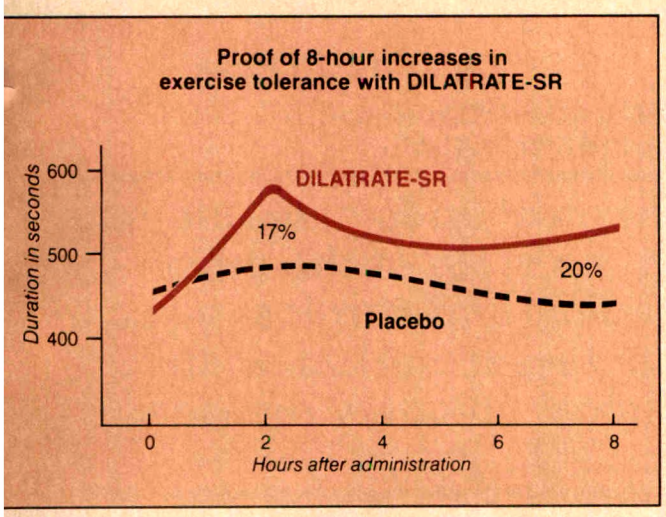

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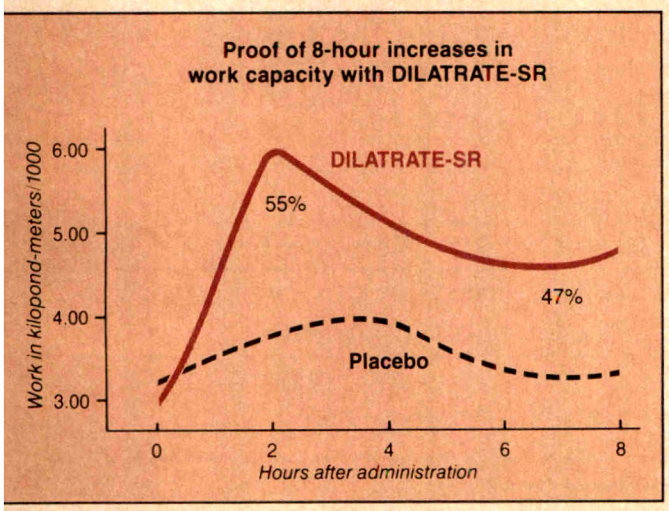

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References:

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Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATION: Idiosyncrasy to this drug.

WARNINGS: Data supporting the use of nitrates and nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

PRECAUTIONS: Tolerance to this drug, and cross-tolerance to other nitrates or nitrites may occur.

In patients with functional or organic gastrointestinal hypermotility or malabsorption syndrome it is suggested that either the 5 mg. or 10 mg. oral tablets or 2.5 mg. or 5 mg. sublingual tablets be the preferred therapy.

ADVERSE REACTIONS: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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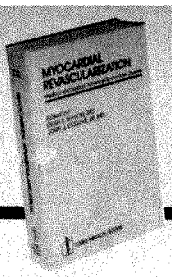

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tions moving from the left atrium to the aorta. The overall incidence of this phenomenon was 49% in 79 patients, and the frequency and extent of microbubble formation was related to the need for cardiotomy, providing an easy source of entry for air. No patient studied manifested evidence of a cerebrovascular accident. It is concluded that 2-dimensional echocardiography is useful in detecting intracardiac microbubbles and therefore may be instrumental in their elimination.

EXPERIMENTAL STUDIES

1133 Impaired Collateral Blood Flow Reserve Early After Nontransmural Myocardial Infarction in Conscious Dogs

RANDOLPH E. PATTERSON, BEVERLY A. JONES-COLLINS, and ROGER AAMODT

The purpose of this study was to determine the adequacy of collateral blood flow reserve of myocardium surviving a nontransmural myocardial infarction. Ventricular pacing increased the heart rate from 110 to 220 beats/min without changing aortic or left atrial pressure 3 to 4 days after occlusion of 2 major coronary arteries in conscious dogs. Subendocardial and mid-myocardial ischemic zone samples contained infarcted tissue and had low control values of coronary vascular conductance (flow/100 mm Hg mean aortic pressure), which tended to decrease during pacing. Coronary vascular conductance in normal zone myocardium increased 35% from control to pacing but did not change in surviving tissue located in the subepicardial layers of collateral-dependent myocardium. Thus, collateral vessels increase blood flow to nearly normal levels by 3 to 4 days after myocardial infarction, but lack reserve capacity to increase blood flow in response to stress.

1141 Relation Between Regional Distribution of Thallium-201 and Myocardial Blood Flow in Normal, Acutely Ischemic, and Infarcted Myocardium

ALAN CHU, ROBERT H. MURDOCK, Jr., and FREDERICK R. COBB

This study compares myocardial localization of thallium-201 with direct measurements of myocardial perfusion in normal, acutely ischemic and recently infarcted myocardium. Studies were performed in 6 chronically instrumented animals subjected to myocardial infarction by occlusion of the proximal left circumflex coronary artery. Four days after myocardial infarction, thallium-201 and 9 $\pm$ 1 μm microspheres were injected simultaneously after acute left anterior descending coronary artery occlusion; the animals were killed 5 minutes later and the entire left ventricle was sectioned into 1 to 2 g samples. Regression analyses between thallium-201 activity and regional myocardial blood flow using all myocardial samples demonstrate a very close linear relation in each dog; r values were 0.98 or greater, indicating that the initial localization of thallium-201 in acutely ischemic and recently infarcted myocardium as a function of regional blood flow was essentially identical.

HISTORICAL STUDIES

1145 Jacob Mendez DaCosta: Medical Teacher, Clinician, and Clinical Investigator

CHARLES F. WOOLEY

J. M. DaCosta was recognized during his lifetime as an authority on physical diagnosis and had an unexcelled reputation as a clinical teacher. Chairman of Medicine at the Jefferson Medical College for 19 years, president of the College of Physicians of Philadelphia in 1884 and again in 1895, he was one of the original members of the Association of American Physicians and its president in 1897. Earlier in his career, his extensive Civil War study of "a form of cardiac malady common among soldiers . . . the study of which is equally interesting to the civil practitioner" was described in his 1871 report "On Irritable Heart; A Clinical Study of a Form of Functional Cardiac Disorder and Its Consequences." Soon labeled *DaCosta's syndrome*, the irritable heart lineage can be traced through the *soldier's heart*, the *effort syndrome*, and *neurocirculatory asthenia* in World War I, *anxiety neurosis* in World War II, and the *mitral valve prolapse syndrome* in the second half of the 20th century.

EDITORIALS

1149 Hypothesis: Is Congestive Cardiomyopathy Caused by a Hyperreactive Myocardial Microcirculation (Microvascular Spasm)?

STEPHEN M. FACTOR and EDMUND H. SONNENBLICK

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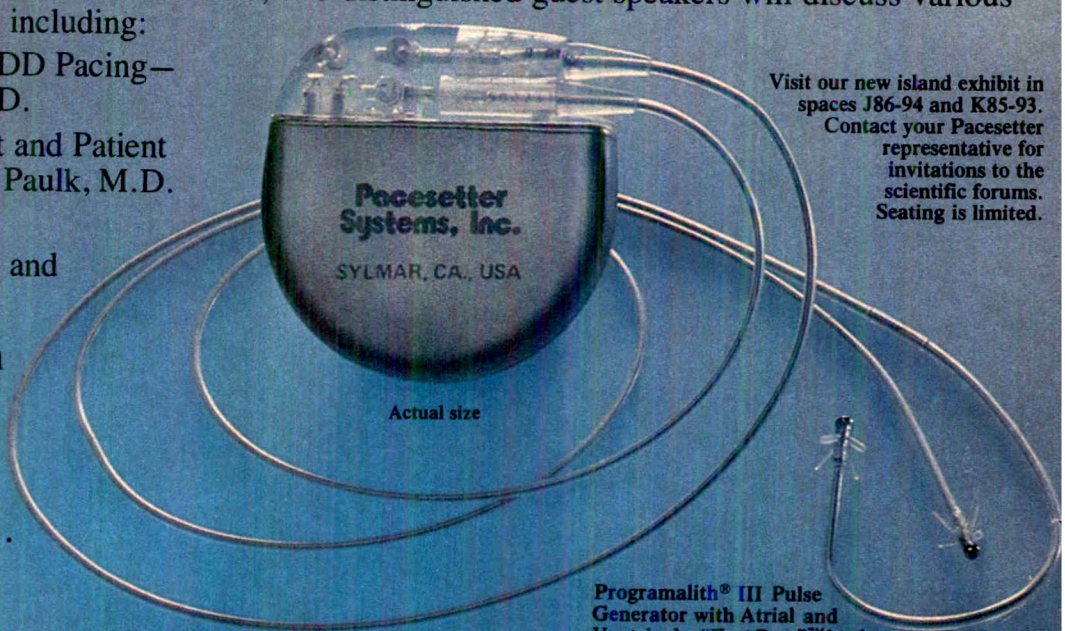

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SYMPOSIUM ON VERAPAMIL THERAPY FOR ANGINA PECTORIS. PART III: STUDIES IN EFFORT-RELATED ANGINA

MILTON PACKER, Guest Editor, and WILLIAM H. FRISHMAN, Guest Co-Editor

1153 Verapamil Therapy for Stable Exertional Angina Pectoris

DONALD A. WEINER and MICHAEL D. KLEIN

The clinical and exercise response to therapy with the calcium-channel blocking agent verapamil was assessed in 26 patients with stable exertional angina pectoris using a double-blind placebo-controlled randomized crossover study design. Verapamil (480 mg daily) reduced the frequency of anginal attacks and the number of nitroglycerin tablets consumed and increased exercise duration compared with placebo. Adverse effects from verapamil were few and consisted primarily of constipation in 6 patients. A total of 193 patients have been entered in 6 independent clinical trials, which have compared verapamil with placebo for the treatment of stable exertional angina pectoris, using a similar study design. The combined evidence from all of these studies indicates that verapamil is a highly effective and safe drug for the treatment of stable effort-related angina pectoris.

1158 Calcium Channel Blockade as Primary Therapy for Stable Angina Pectoris. A Double-Blind Placebo-Controlled Comparison of Verapamil and Propranolol

V. BALA SUBRAMANIAN, MICHAEL J. BOWLES, ANTHONY B. DAVIES, and EDWARD B. RAFTERY

The effectiveness and safety of the beta-adrenergic blocking agent propranolol and the calcium channel antagonist verapamil were studied using a placebo-controlled, double-blind, randomized crossover protocol in 22 patients with chronic stable angina pectoris. Both verapamil and propranolol increased exercise tolerance, but the increase with verapamil was significantly greater. Both drugs prolonged the exercise duration to 1 mm of S-T depression to a similar degree; both drugs decreased the resting heart rate, but the rate decreased more with propranolol than with verapamil. Neither drug produced significant adverse reactions. This study, along with 8 similar double-blind placebo-controlled randomized investigations comparing verapamil with propranolol, indicate that verapamil is as effective and safe as propranolol in relieving symptoms and improving exercise tolerance in patients with chronic stable angina pectoris.

1164 Comparison of Oral Propranolol and Verapamil for Combined Systemic Hypertension and Angina Pectoris. A Placebo-Controlled Double-Blind Randomized Crossover Trial

WILLIAM H. FRISHMAN, NEAL A. KLEIN, PHILIP KLEIN, JOEL A. STROM, ROBERT TAWIL, ROGER STRAIR, BOWEN WONG, STEVEN ROTH, THIERRY H. LeJEMTEL, SIMCHA POLLACK, and EDMUND H. SONNENBLICK

The relative effectiveness of verapamil and propranolol were compared in 12 patients with both stable angina pectoris and mild to moderate systemic hypertension, using a placebo-controlled, double-blind, randomized crossover protocol. Both propranolol and verapamil produced a similar decrease in the frequency of anginal attacks and a similar increase in exercise duration. Both drugs reduced supine and standing systolic and diastolic blood pressure measured at rest; however, verapamil had greater effects on standing diastolic blood pressure than propranolol. Plasma renin activity was increased by verapamil but was reduced by propranolol; neither drug altered plasma aldosterone levels. Verapamil appears to be a safe and effective alternative to propranolol for improving exercise tolerance and reducing elevated systemic blood pressure in patients with both angina pectoris and systemic hypertension.

1173 Rationale for the Choice of Calcium Antagonists in Chronic Stable Angina. An Objective Double-Blind Placebo-Controlled Comparison of Nifedipine and Verapamil

V. BALA SUBRAMANIAN, MICHAEL J. BOWLES, NARDEV S. KHURMI, ANTHONY B. DAVIES, and EDWARD B. RAFTERY

The effectiveness and safety of verapamil, nifedipine, and placebo in patients with chronic stable angina pectoris were compared in 2 clinical trials. In the first study, nifedipine (30 mg daily) did not differ from placebo in 24 patients with exertional anginal symptoms. In the second study, verapamil (360 mg daily), nifedipine (60 mg daily), and placebo were compared in 32 patients with chronic stable angina using a double-blind crossover study design. Compared with placebo, both nifedipine and verapamil prolonged exercise duration, but the im-

Continued on Page A67

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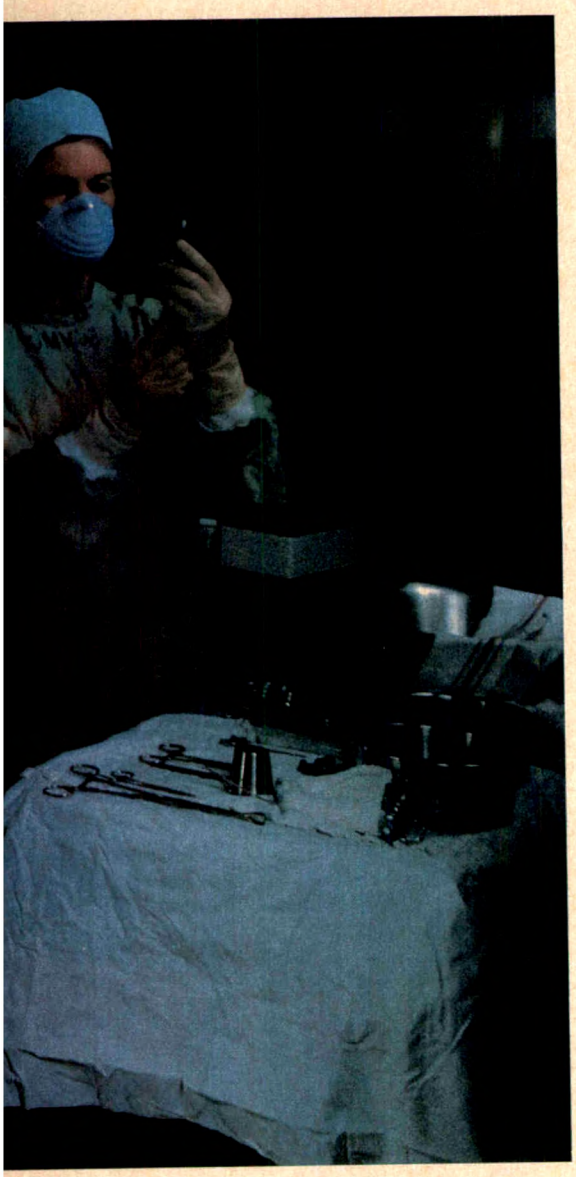

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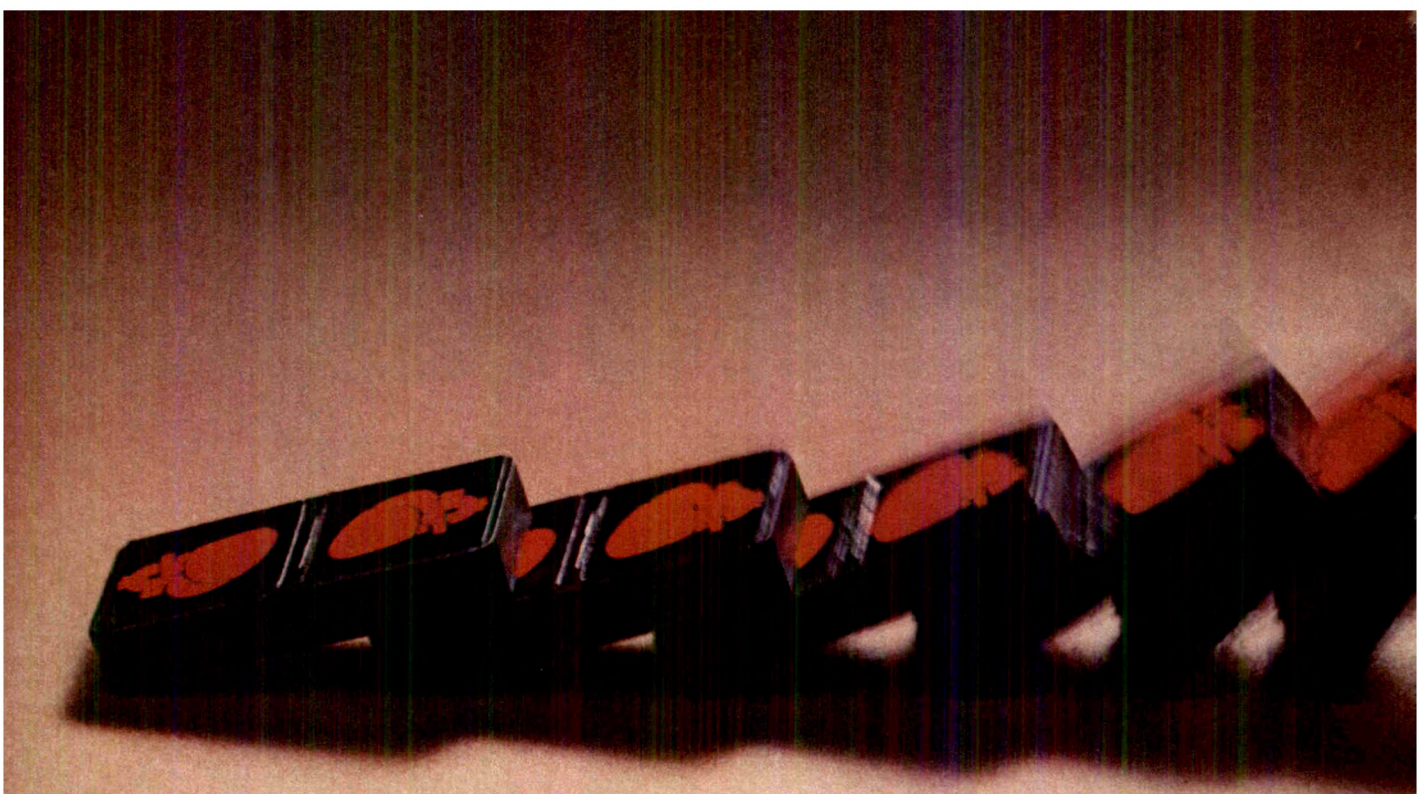

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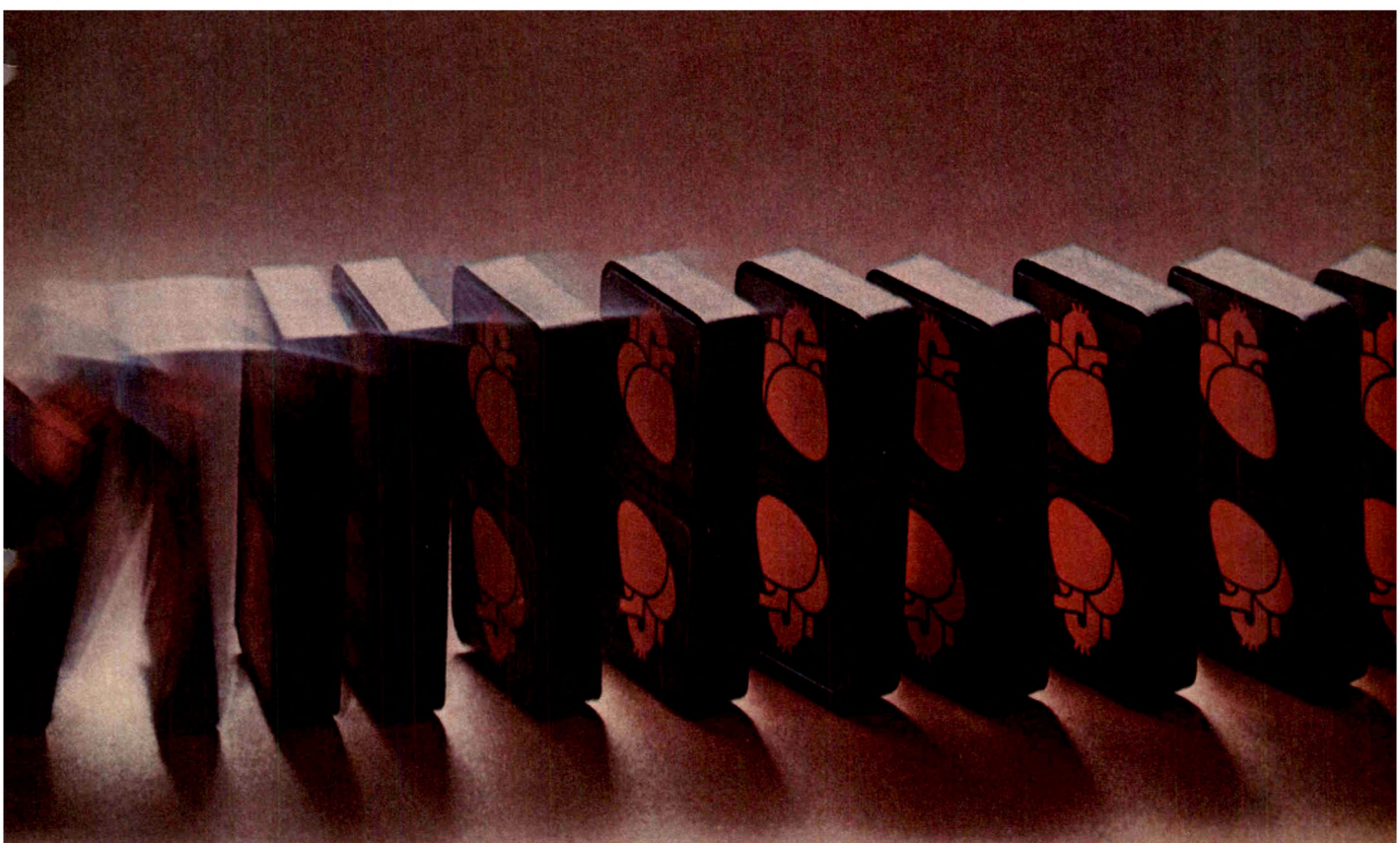

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CONTRAINDICATIONS

1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless it is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE. In congestive heart failure, inhibition with beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In patients already receiving digitalis, propranolol may reduce the positive inotropic action of digitalis and may have an additive depressant effect on AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, in rare instances, cardiac failure has developed during propranolol therapy. At the first sign of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and observed closely. a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Give special consideration to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol should be withdrawn slowly, since abrupt withdrawal may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta-blockade impairs the ability of the heart to respond to reflex stimuli. Except in pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery. In case of emergency surgery, the effects of propranolol can be reversed by administration of beta-receptor agonists such as isoproterenol or levarterenol, but such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), administer with caution, since propranolol may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA. Propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in patients with labile diabetes. A precipitous elevation of blood pressure may accompany hypoglycemic attacks.

USE IN PREGNANCY: Safe use in human pregnancy not established. Embryotoxic effects have been seen in animals at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if propranolol is administered, since it may occasionally produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

Observe laboratory parameters at regular intervals. Use with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta-blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

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provement with verapamil was greater than with nifedipine. Seven patients had increasing angina while on nifedipine, but none did while on verapamil; this appeared related to the higher heart rates with nifedipine than with placebo. At the doses used, verapamil was more effective and was better tolerated than nifedipine in patients with chronic stable angina pectoris.

1180 Clinical Relevance of Verapamil Plasma Levels in Stable Angina Pectoris

WILLIAM FRISHMAN, EDWARD KIRSTEN, MICHAEL KLEIN, MICHAEL PINE, STACEY M. JOHNSON, L. DAVID HILLIS, MILTON PACKER, and ROBERT KATES

In 77 patients who received verapamil for treatment of angina pectoris, there was a sixfold interpatient variation in verapamil plasma concentrations, but plasma concentrations were linearly related to doses of the drug (240 to 480 mg/day) in the same patient. Although verapamil produced a significant improvement in exercise tolerance in most patients, the increase in exercise time was not related to plasma levels of the drug; an increase in the dose of verapamil for 320 to 480 mg daily produced a 71% increase in plasma levels of the drug but no significant increase in exercise tolerance. Despite the high plasma drug levels, the average increase in P-R interval with 480 mg of verapamil was only 8% (161 at 18 to 174 at 22 ms), and only 6 patients had first-degree heart block. Determination of plasma levels of verapamil are of limited value in the management of patients with angina pectoris.

1185 Long-Term Effectiveness of Verapamil in Stable and Unstable Angina Pectoris. One-Year Follow-Up of Patients Treated in Placebo-Controlled Double-Blind Randomized Clinical Trials

STEPHEN SCHEIDT, WILLIAM H. FRISHMAN, MILTON PACKER, JAWAHAR MEHTA, OBERDAN PARODI, and V. BALA SUBRAMANIAN

The clinical responses to 12 months' treatment with verapamil were evaluated in 63 patients with stable and unstable angina pectoris in whom the effectiveness of verapamil had been established in short-term double-blind placebo-controlled clinical trials. In 41 patients with effort-related angina, verapamil produced a sustained reduction in the frequency of anginal attacks and consumption of nitroglycerin for periods exceeding 1 year; this prolonged improvement was confirmed by serial treadmill exercise testing in 21 patients. In 22 patients with unstable angina at rest, verapamil produced a sustained amelioration of anginal symptoms. However, the incidence of death and myocardial infarction remained high and was similar to that previously reported in large clinical studies using either combinations of verapamil and nitrates, nifedipine and propranolol, or propranolol and nitrates.

1191 Comparative Effects of Abrupt Withdrawal of Propranolol and Verapamil in Angina Pectoris

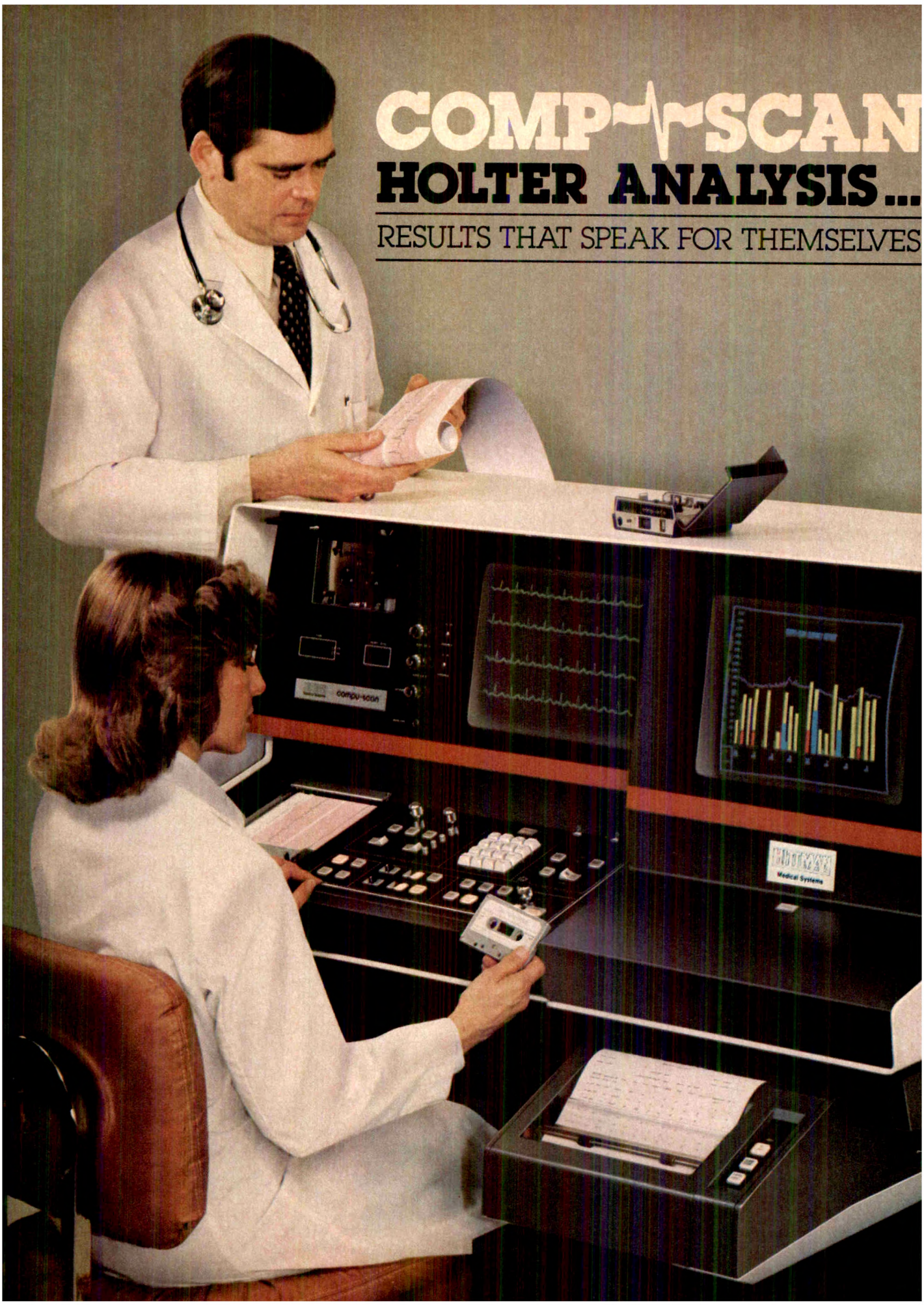
WILLIAM H. FRISHMAN, NEAL KLEIN, JOEL STROM, MARTIN N. COHEN, HARRY SHAMOON, HOWARD WILLENS, PHILIP KLEIN, STEVEN ROTH, LOUIS IORIO, THIERRY LEJEMTEL, SIMCHA POLLACK, and EDMUND H. SONNENBLICK

The comparative effects of withdrawal from long-term administration of propranolol and verapamil were assessed in a placebo-controlled double-blind randomized crossover study of 20 patients with stable angina pectoris. All 20 patients were withdrawn from verapamil without evidence of a rebound increase in frequency of anginal attacks, blood pressure, heart rate, and rate-pressure product, and without a rebound deterioration in exercise tolerance. In contrast, with propranolol withdrawal, 2 patients (with the highest baseline rate of anginal attacks) had a severe exacerbation of the anginal syndrome and could not undergo exercise; the other 18 patients were withdrawn from propranolol without incident. Plasma catecholamine levels were increased with exercise compared with rest during all treatments; however, the catecholamine levels during exercise were significantly higher with propranolol than with verapamil and placebo.

SPECIAL DEPARTMENTS

1196 Instructions to Authors

1197 Letters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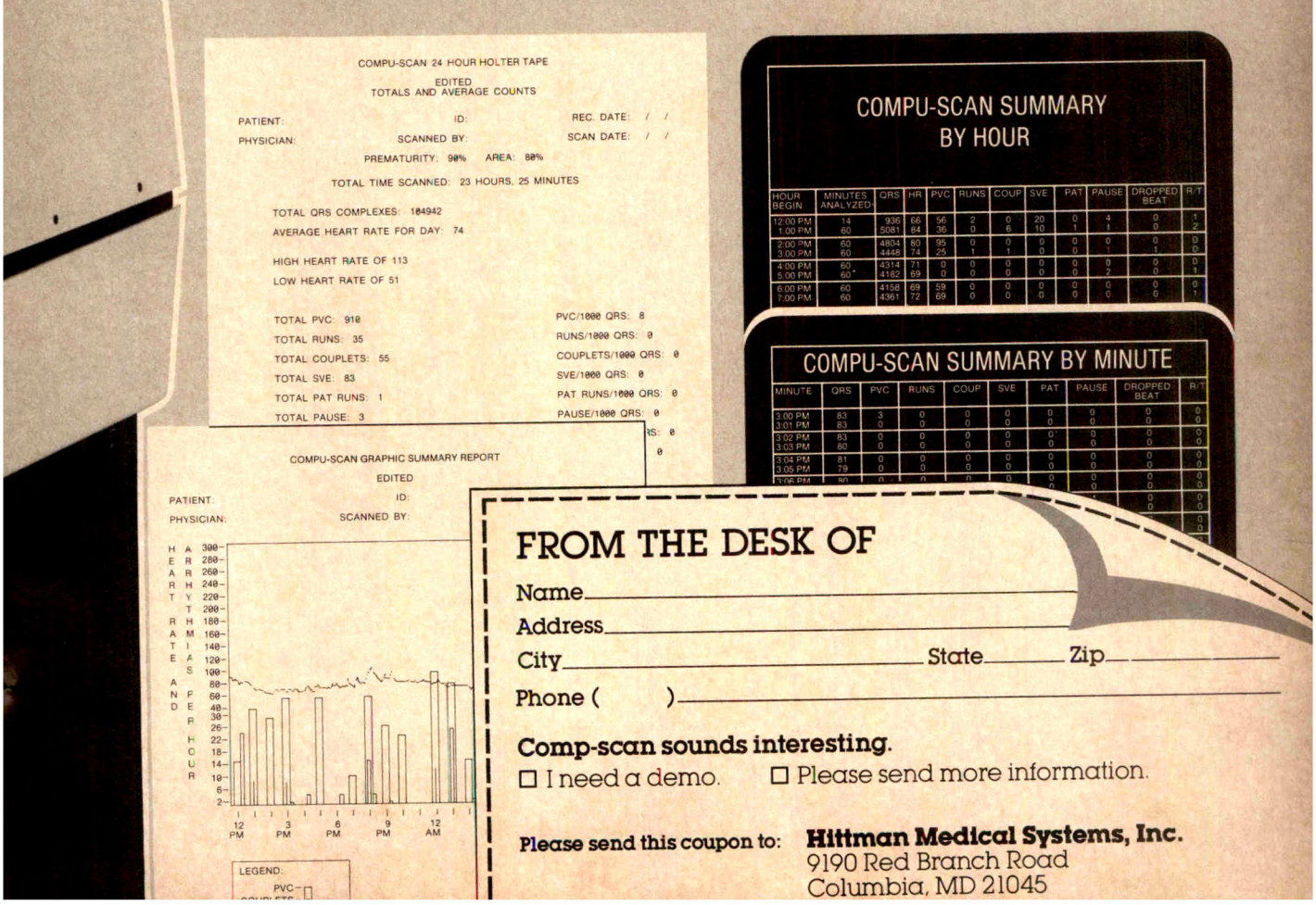

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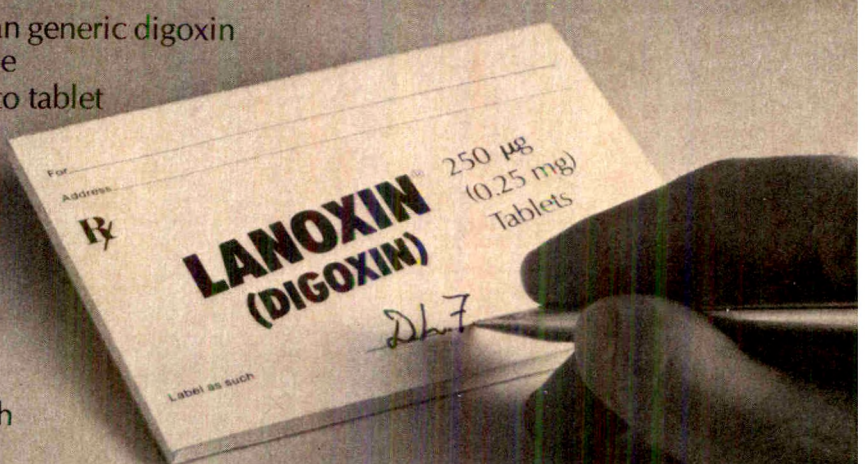

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VOLUME 50

NUMBER 5

CLINICAL STUDIES

Intracoronary Thrombolysis in Acute Myocardial Infarction: Duration of Ischemia as a Major Determinant of Late Results After Recanalization

FRANZ SCHWARZ, MD, GERHARD SCHULER, MD, HUGO KATUS, MD, MANFRED HOFMANN, MD, JOACHIM MANTHEY, MD, HARALD TILLMANNS, MD, HELMUTH C. MEHMEL, MD, and WOLFGANG KÜBLER, MD

To define the effect of duration of myocardial ischemia on the late results after successful thrombolysis in patients with acute transmural myocardial infarction, data on 39 patients treated with intracoronary infusion of streptokinase were analyzed. Patients with successful recanalization of infarct vessel and a time lag between onset of symptoms and reperfusion less than 4 hours were assembled in group A1 (n = 15), and patients with successful recanalization but a time lag of more than 4 hours (n = 17) in group A2. Group B consisted of 7 patients with unsuccessful thrombolysis. Coronary anatomy, left ventricular volume, ejection fraction, and regional ejection fraction of infarct area were determined before and 4 weeks after thrombolysis with cineangiography. Serum creatine kinase activity was serially measured.

Before intervention, the groups were comparable with regard to age, Killip class, localization of infarction, incidence of previous infarction, Gensini score of coronary anatomy, left ventricular volume, ejection fraction, regional ejection fraction of infarct area, and serum creatine kinase activity. Four weeks after the intervention, patients in group A1 had a higher ejection fraction (59%) and regional ejection fraction of infarct area (39%) than patients in group A2 (ejection fraction: 49%, $p < 0.05$; regional ejection fraction: 26%, $p < 0.05$) and group B (ejection fraction: 44%, $p < 0.05$; regional ejection fraction: 25%, $p = 0.05$). Peak serum creatine kinase activity measured during the acute illness was lower in group A1 (764 U/liter) than in group A2 (1,580 U/liter, $p < 0.05$) and group B (2,106 U/liter, $p < 0.05$).

Thus, contraction of infarct area was improved and enzymatic estimate of infarct size was reduced after early as compared with late reperfusion in patients with acute myocardial infarction.

The beneficial effect of coronary arterial reperfusion in acute transmural myocardial infarction is critically dependent on the duration of coronary occlusion.[1-3] Nonsurgical reperfusion has been established by use of intracoronary thrombolysis by streptokinase infusion in patients with acute myocardial infarction.[4,5] Improvement of left ventricular function was documented after thrombolysis as measured with the ejection fraction.[6] The effect of the duration of myocardial ischemia on contraction of infarct area and enzymatic estimate of infarct size is not yet well defined. Therefore the aim of the present study was to assess the effects of early reperfusion (within 4 hours after onset of symptoms) and late reperfusion (more than 4 hours after onset of symptoms) on left ventricular function and enzymatic estimate of infarct size.

From the Abteilung Innere Medizin III (Kardiologie) der Medizinischen Universitätsklinik Heidelberg, West Germany. This study was supported by a grant from the Deutsche Forschungsgemeinschaft, Bonn-Bad Godesberg, SFB 90 Kardiovaskuläres System, University of Heidelberg, Heidelberg, West Germany. Manuscript received February 22, 1982; revised manuscript received May 17, 1982, accepted May 26, 1982.

Address for reprints: Franz Schwarz, MD, Abteilung Innere Medizin III (Kardiologie), Medizinische Universitätsklinik, Bergheimer Strasse 58, 6900 Heidelberg, West Germany.

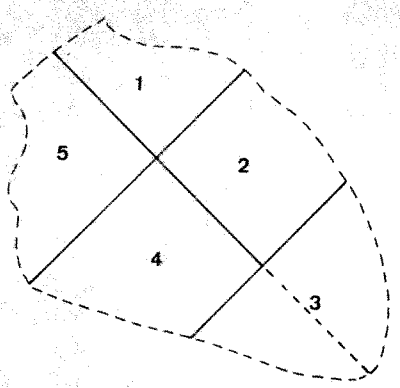

FIGURE 1. Right anterior oblique ventriculogram showing the 5 areas analyzed. Systolic contraction was measured as percent area reduction. For anterior infarction areas 1, 2, and 3 were averaged; for inferior infarction areas, 3, 4, and 5.

Methods

Patients: Thirty-nine patients with acute transmural myocardial infarction, in whom intracoronary infusion with streptokinase was performed in order to recanalize the obstructed coronary artery, were studied. These patients were selected from a consecutive series of 62 patients who underwent intracoronary thrombolysis because they had a second invasive study after 4 weeks. Five of the remaining 23 patients died during the acute phase of their disease and therefore could not be restudied, and 18 patients refused the second invasive study. The diagnosis of transmural myocardial infarction was based on (1) acute chest pain lasting for more than 30 minutes, (2) persistent S-T segment elevation (greater than 2 mm in at least 3 leads of the standard 12 lead electrocardiogram) lasting for more than 30 minutes and progressing to new Q waves. Those not accepted in the study were (1) patients who had symptoms of more than 12 hours at entry into the coronary care unit, (2) patients with recurrent infarction of a previously infarcted area, and (3) patients older than 75 years. No patient was excluded from invasive therapy because of poor hemodynamic condition. All patients gave written informed consent after detailed explanation of the procedure, its possible hazards, and possible beneficial effects.

Cardiac catheterization: Patients were studied with selective coronary arteriography using the femoral percutaneous technique. They were given heparin, 7,500 U intraarterially, and prednisolone, 250 mg intravenously, in order to prevent allergic reactions to streptokinase. Diazepam and morphine sulfate were administered when necessary. Before use of contrast material left ventricular pressure was recorded during mid-inspiratory apnea (8F catheter, Statham P23db transducer). Monoplane left ventricular cineangiography was performed in the 30° right anterior oblique projection (40 ml Urografin 76®, 35 mm cinefilm, 50 frames/s, Philips dual field 9-5 inch image intensifier system). Selective arteriography of the right and left coronary artery (by manual injection) was performed in 6 projections including 3 hemiaxial projections. When a coronary occlusion was clearly visualized, intracoronary injection of 0.2 to 0.4 mg of nitroglycerin was performed to exclude spastic occlusion; thereafter continuous infusion of streptokinase (2,000 U/min) was begun with the coronary catheter in the coronary ostium. Contrast material injections were repeated every 15 minutes and the infusion was stopped 15 minutes after reperfusion. If the coronary vessel was not reopened after infusion of 200,000 U of streptokinase, the attempt was given up. Thereafter the patient was transferred to the coronary care unit.

Patient care: Patients were treated with bed rest. Administration of intravenous heparin was begun according to thrombin time to achieve therapeutic anticoagulation (prolongation of thrombin time to 2 to 3 times normal value). This therapy was followed by oral sodium warfarin. A routine 12

TABLE I Baseline Clinical and Hemodynamic Characteristics

	Group A1 (Early Reperfusion)	Group A2 (Late Reperfusion)	Group B (No Reperfusion)
Cases (n)	15	17	7
Time between onset of symptoms and reperfusion	3:10 ± 0:56	5:52 ± 1:51	. . .
Age (mean ± standard deviation)	55 ± 10	55 ± 10	50 ± 9
Male sex (%)	87	88	100
Killip class (mean ± SD)	1.33 ± 0.62	1.41 ± 0.71	1.29 ± 0.76
Infarction (%)			
Anterior	53	41	43
Inferior	47	59	57
History of previous infarction (%)	13	12	14
Gensini score			
All coronary vessels	53.4 ± 17.3	46.8 ± 29.8	51.1 ± 17.9
Infarct vessel	40.0 ± 21.6	37.5 ± 22.2	40.0 ± 12.7
Infarct vessel (%)			
Left anterior descending branch	53	41	42
Left circumflex branch	0	18	29
Right coronary artery	47	41	29
Angiographically visible collateral supply to infarct vessel (%)	50	44	71
Heart rate (min^{-1})	74.4 ± 13.8	89.8 ± 16.3*	86.6 ± 18.6
Left ventricular systolic pressure (mm Hg)	122.7 ± 22.2	124.7 ± 21.9	119.7 ± 27.4
Left ventricular end-diastolic pressure (mm Hg)	20.4 ± 6.6	23.5 ± 7.4	16.7 ± 7.8
Left ventricular end-diastolic volume (ml/m^2)	84.9 ± 17.8	93.5 ± 15.3	86.6 ± 13.9
Ejection fraction (%)	49.0 ± 10.2	43.9 ± 9.9	48.9 ± 13.1
Regional ejection fraction of infarct area (%)	23.9 ± 9.3	22.1 ± 9.2	27.4 ± 7.4
Regional ejection fraction of normal area (%)	45.1 ± 13.6	44.7 ± 16.0	39.4 ± 19.5
Serum creatine kinase activity (U/liter)	45.2 ± 19.5	60.3 ± 45.3	51.9 ± 18.7
Time between onset of symptoms and start of cardiac catheterization	2:28 ± 0:57	4:55 ± 2:00*	4:00 ± 1:42

* $p < 0.05$ versus value in group A1.

lead electrocardiogram was obtained daily in the coronary care unit. Serum creatine kinase activity was determined hourly for 12 hours and every 4 hours for the following 36 hours.[8] (The normal range of serum creatine kinase activity is up to 80 U/liter.[8]) Patients left the coronary care unit after 4 to 5 days. Left ventricular and coronary angiography were repeated 4 weeks after the acute event using premedication with diazepam, 10 mg orally. Great care was taken to obtain identical views of left ventricular angiograms at baseline and after 4 weeks (the C-arm was equipped with a scale of 360°). Patients were discharged from the hospital 1 day later.

Analysis of angiograms: The angiograms were interpreted independently by 2 experienced observers. From the coronary arteriograms obstructions were determined and collateral circulation to the distal vessel segment (the infarct vessel before recanalization) was carefully noted. Coronary anatomy was scored as suggested by Gensini,[9] and scores were calculated for all coronary vessels and for the infarct vessel. Estimates of the severity of coronary anatomy by 2 observers were highly correlated ($r = 0.90$, $n = 60$). End-diastolic, end-systolic, and stroke volumes were determined[10] from the left ventricular angiograms, and both the ejection fraction and the regional ejection fraction were calculated. The regional ejection fraction was determined with use of the area method of Gelberg et al.[11] The area system measured systolic change as area reduction (in percent of end-diastolic area). Areas corresponding to the perfusion area of the infarct vessel were averaged (anterior infarction: areas 1, 2, and 3; inferior infarction: areas 3, 4, and 5 [Fig. 1]). Normal areas were also averaged. To minimize bias in the tracing of the ventriculogram for a patient after 4 weeks, outlines were obtained in early and late batches with the patient order randomized in each batch. The early ejection fraction was measured by 2 experienced observers independently in 15 patients (without clinical and arteriographic outcome), and comparison of data revealed a correlation coefficient of $r = 0.93$. The regional ejection fraction was measured in 26 regions by the same 2 independent observers, and results showed a correlation coefficient of 0.93. Left ventricular end-diastolic pressure was measured at the junction of the a wave with the upstroke of ventricular pressure.

Statistical analysis: Analysis of variance, the Student-Newman-Keuls test, and the chi-square procedure (Brandt-Snedecor) were used.[12] Differences were considered significant if the probability (p) was less than 0.05. Mean values ± standard deviation are given in the tables and the Results section.

Results

Comparability of groups: Fifteen patients had successful recanalization of the infarct vessel within 4 hours (group A1) after the onset of symptoms, 17 patients had recanalization after more than 4 hours (group A2), and in 7 patients the attempt to recanalize failed (group B). The average age of patients in group A1 (2 women, 13 men) was 55 ± 10 years, in group A2 (2 women, 15 men) 55 ± 10 years, and in group B (7 men) 50 ± 9 years (Table I). At initial clinical examination 11 patients in group A1 were in Killip class I, 3 were in class II, and 1 was in class III[7]; 12 patients in group A2 were in class I, 3 in class II, and 2 in class III; and 6 patients in group B were in class I and 1 patient was in class III. One patient had cardiogenic shock (characterized by central systolic arterial blood pressure less than 90 mm Hg, evidence of peripheral hypoperfusion, urinary flow below 20 ml/hour, pulmonary wedge pressure of 15 mm Hg or greater, and a cardiac index of 2.3 liters/min per m^2 or less) within 24 hours after the onset of symptoms. Anterior, anterolateral, and anteroseptal infarctions were categorized as anterior infarctions and were found in 8, 7, and 3 patients of groups A1, A2, and B, respectively; inferior, inferolateral, and inferoposterior infarctions were categorized as inferior infarctions and were found in 7, 10, and 4 patients of groups A1, A2, and B (Table I). A history of previous infarction was present in 2 patients each in groups A1 and A2 and in 1 patient in group B.

The time lag between onset of symptoms and recanalization of infarct vessel was 3 hours 10 minutes in group A1 and 5 hours 52 minutes in group A2. The baseline Gensini score for all coronary vessels and for the infarct vessel, localization of the infarct vessel, collateral supply to the infarct vessel, left ventricular pressure, left ventricular end-diastolic volume, ejection fraction, regional ejection fraction of the infarct area, and serum creatine kinase activity were comparable among the 3 groups (Table I). The heart rate at the beginning of cardiac catheterization was significantly higher ($p < 0.05$) in group A2 than in group A1. In group A1, 11 of 15 patients had total occlusion of the infarct

TABLE II Follow-Up Data 4 Weeks After Thrombolysis

	Group A1 (Early Reperfusion)	Group A2 (Late Reperfusion)	Group B (No Reperfusion)
Cases (n)	15	17	7
Dose of streptokinase used (IU)	145,000 ± 46,200	173,500 ± 42,200	210,000 ± 19,200
Gensini score (all coronary vessels)	22.1 ± 17.9	20.8 ± 28.8	41.4 ± 19.9
Gensini score (infarct vessel)	8.7 ± 7.2	7.9 ± 8.7	30.3 ± 14.6*,†
Heart rate (min^{-1})	67.5 ± 11.6	82.5 ± 14.1*	84.7 ± 13.4*
Left ventricular systolic pressure (mm Hg)	127.0 ± 14.0	122.1 ± 16.9	120.0 ± 22.8
Left ventricular end-diastolic pressure (mm Hg)	15.8 ± 4.8	14.8 ± 7.5	17.6 ± 9.7
Left ventricular end-diastolic volume (ml/m^2)	92.3 ± 17.1	100.9 ± 23.6	77.4 ± 9.1†
Ejection fraction (%)	58.9 ± 12.3	49.1 ± 13.2*	44.1 ± 11.9*
Regional ejection fraction of infarct area (%)	39.0 ± 15.8	26.4 ± 13.4*	24.6 ± 9.9
Regional ejection fraction of normal area (%)	45.8 ± 13.7	48.7 ± 16.4	36.9 ± 23.1
Peak serum creatine kinase activity (U/liter)	764 ± 403	1,580 ± 877*	2,106 ± 1,699*

* $p < 0.05$ versus value in group A1. † $p < 0.05$ versus value in group A2.

vessel but 4 had subtotal occlusion (99%) with poor runoff. Success was defined as reopening of occlusion with good runoff or marked improvement of runoff in cases of subtotal occlusion. In group A2, 13 of 17 patients had total occlusion and 4 patients subtotal occlusion of the infarct vessel ($p > 0.05$).

Duration of ischemia versus late results 4 weeks after thrombolysis: At restudy in group A1, the recanalized infarct vessel was found open (but stenosed) in 12 of 15 patients; the patient with early bypass grafting had an open graft, and the remaining 2 patients who had reinfarction showed reocclusion of the infarct vessel. In group A2 the infarct vessel was open (with stenosis) in 12 patients; the 2 patients with early bypass grafting had an open graft, the patient with early transluminal angioplasty had 50% stenosis, and 2 patients had reocclusion of the infarct vessel. In group B, 1 of 7 patients had spontaneous recanalization of the infarct vessel at restudy, but the remaining 6 patients had an occluded infarct vessel.

The Gensini score of the infarct vessel was significantly lower after 4 weeks in groups A1 and A2 after recanalization than in group B (Table II). The ejection fraction was significantly higher in group A1 than in the other 2 groups. Similarly, the regional ejection fraction of the infarct area was higher in group A1 than in both the other groups (Table II). Serum peak creatine kinase activity increased from group A1 to group A2 and group B (Table II). The dose of streptokinase, the Gensini score of all coronary vessels, left ventricular pressure, and the regional ejection fraction of the normal area did not differ between groups. Left ventricular end-diastolic volume was lower in group B than in group A2.

Hospital course and late follow-up study: Patients were hospitalized for 4 weeks after infarction. Recurrence of infarction by clinical and enzymatic criteria was observed in 2 patients in group A1 and in 2 patients in group A2. The interval between initial infarction and recurrence of infarction was 1 day, respectively, 7 days in group A1 and 10, respectively, 15 days after initial infarction in group A2. Coronary bypass surgery was performed the day after successful recanalization in 1 patient in group A1 and in 2 in group A2. Percutaneous transluminal angioplasty was performed in 1 patient in group A2 two days after successful recanalization. Complications of the procedure were minor bleeding at the puncture site in 4 patients and gastrointestinal bleeding in 1 patient. The patients in group A1 were followed up for 13.9 ± 5.8 months (range 6 to 24), patients in group A2 for 9.9 ± 7.6 months (range 2 to 23), and patients in group B for 11.0 ± 3.2 months (range 7 to 16). Five patients in group A1 and 2 in group A2 had undergone aortocoronary bypass because of disabling angina 2 to 6 months after infarction. No patient in group A1 but 3 patients in group A2 and 1 in group B died during the late follow-up period.

Discussion

The data of the present study show that reperfusion after a short duration of ischemia (group A1) exerts a beneficial effect: A higher ejection fraction, regional ejection fraction of the infarct area, and a lower serum peak creatine kinase activity were found in this group than in the group with reperfusion after a long duration of ischemia (group A2), or in the group without reperfusion (group B). The 3 groups were comparable according to the following criteria: (1) the state of coronary vessels, especially of the infarct vessel as evaluated by the Gensini score; (2) the localization of infarctions; (3) regional and overall left ventricular function as determined by invasive study; (4) clinical class at entry into the coronary care unit; and (5) normal serum creatine kinase activity before invasive study. Thus, comparability of the 3 groups before thrombolytic therapy was documented by invasive and noninvasive data.

The diagnosis of acute transmural myocardial infarction was mainly based on persistent S-T segment elevation and development of new Q waves. DeWood et al.[2] found that persistent (as opposed to transient) major S-T segment elevation greater than 2 mm led to transmural infarction (as estimated from the development of new Q waves) in more than 98% of 232 patients. The present study accepted only patients with S-T segment elevation of at least 2 mm in at least 3 leads of the standard 12 lead electrocardiogram persisting for more than 30 minutes.

In experimental studies it has been shown that infarct size was determined by (1) the duration of ischemia,[3] (2) the collateral flow to ischemic area,[13] and (3) the size of the perfusion area of the infarct vessel.[14,15] The present study assessed differences in the duration of ischemia (coronary occlusion) before reperfusion in a series of patients in whom collateral flow to the ischemic area and size of the perfusion area as estimated by the Gensini score were found comparable. The duration of ischemia is a major determinant of infarct size and early mortality after coronary arterial reperfusion in dogs.[3,16] Various studies have estimated myocardial infarct size and myocardial function after different time lags between coronary occlusion and reperfusion. Most studies report salvage of ischemic myocardium after coronary arterial reperfusion when compared with animals with permanent coronary arterial ligation. The recovery of myocardial function after early reperfusion (1, 2, or 3 hours after coronary occlusion) was protracted and was generally seen only 1 to 4 weeks after the start of reperfusion, but not immediately thereafter.[17–20] When late reperfusion was instituted after 5 or 6 hours of coronary occlusion, recovery of myocardial function was only minimal.[21] When pigs were studied instead of dogs, the beneficial effect of early reperfusion (after 1 hour of coronary arterial occlusion) was less pronounced: Althaus et al.[22] reported no significant difference in infarct size after coronary occlusion in the pig when reperfusion was instituted after 1 hour of coronary occlusion, but only less aneurysmal formation than in animals with permanant coronary occlusion. This lack of a beneficial effect on infarct size was attributed to the lack of adequate collateral circulation in the pig.

Coronary collateral vessels were found in the present study in about 50% of cases in all 3 groups. The collateral supply to ischemic myocardium modifies the association

between the duration of myocardial ischemia and necrosis because collateral flow improves the tolerance of the myocardium against ischemia.[13]

The size of the perfusion area was assessed by the Gensini score, which incorporates the size of territory of a coronary vessel. The Gensini score of the infarct vessel was comparable among the 3 groups, suggesting comparable areas at risk.

Differences in peak creatine kinase activity showed inverse behavior as compared with differences in regional ejection fraction of the infarct area 4 weeks after thrombolysis: Patients with early reperfusion (group A1) had a higher regional ejection fraction and lower peak creatine kinase activity than patients with late reperfusion (group A2). The same was true when data in groups A1 and B were compared. Peak creatine kinase activity was taken as an estimate of myocardial necrosis after reperfusion, because close agreement between enzymatic and histologic extent of infarction was described after experimental reperfusion of infarction.[23] Creatine kinase activity may be disproportionally elevated after reperfusion at a given infarct size as compared with permanent occlusion. Irrespective of these differences in the washout of enzymes, it is evident from the data that early reperfusion produces smaller enzymatic estimates of infarct size than does late reperfusion.

Limitations and implications of the study: The beneficial effect of early reperfusion within 4 hours was shown by comparison with a group that was reperfused after 4 hours of ischemia. Early reperfusion produced smaller infarcts (creatine kinase activity) and better contraction of the infarct region than late reperfusion. Whether late reperfusion has any beneficial effect cannot be answered by the present study: there were only small differences between the group with late reperfusion and the group without reperfusion.

The present study is retrospective. Although the 3 groups are similar in a number of clinical variables and angiographic data, some possible errors cannot be ruled out: Patients who could not undergo recanalization may represent a different type of coronary occlusion (intimal hemorrhage or dissection) than patients who could undergo recanalization (thrombosis). Furthermore, patients who had early reperfusion had a lower heart rate than patients with late reperfusion, and hence myocardial oxygen consumption during occlusion may have been lower in these patients. Because the data presented showed such a highly significant and clinically relevant reduction in infarct size after early as compared with late reperfusion (and permanent coronary occlusion), we do not feel encouraged to undertake a randomized trial to examine more precisely the duration of ischemia before reperfusion versus late results in patients with acute transmural myocardial infarction suited for thrombolysis. Randomization would require postponement of the recanalization attempt in several patients. However, the data presented show that the time lag between the onset of symptoms and reperfusion is clinically the most important determinant of the therapeutic success of recanalization in acute transmural myocardial infarction.

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Sulfinpyrazone Decreases Epinephrine-Induced Platelet Aggregation After Myocardial Infarction

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Platelet studies were performed during a controlled double-blind randomized clinical trial of sulfinpyrazone (Anturane Reinfarction Trial) in 41 patients who had recent myocardial infarction. Aggregation of platelet-rich plasma by thrombin (0.185, 0.246 U/ml), collagen, adenosine diphosphate, and adrenaline (0.23, 0.46, and 0.91 μg/ml) was estimated after a 12 hour fast including abstinence from drugs and cigarette smoking. The tests were carried out 2 weeks after myocardial infarction and 6, 12, and 24 months later. At the last visit, washed platelet suspensions were also tested for aggregation to thrombin (0.03, 0.015 U/ml) ± epinephrine (0.55 μg/ml) and their production of malonyldialdehyde was estimated. A significant ($p < 0.02$) reduction (50%) of the aggregation response of platelet-rich plasma to epinephrine was found in the group treated with sulfinpyrazone ($n = 21$) as compared with the placebo group ($n = 20$). Also, adrenaline evoked a milder ($p < 0.01$) potentiation of aggregation by thrombin of the washed platelet suspensions in the sulfinpyrazone versus the placebo group. Other assays including platelet coagulant activity were not useful in discriminating between the 2 groups. It is concluded that sulfinpyrazone (200 mg 4 times daily) normalizes the platelet response to epinephrine; a relation with the drug-reported reduction of sudden death after myocardial infarction is suggested.

Platelet involvement in vascular and thrombotic processes is well recognized, and the potential benefits of drugs interfering with platelet function have led to several clinical trials in the last decade.[1] Sulfinpyrazone has received special attention in this regard. In contrast to aspirin, sulfinpyrazone reduces platelet turnover and prolongs platelet survival in patients with gout,[2] prosthetic heart valves,[3] mitral valve prolapse,[4] coronary artery disease,[5] rheumatic heart disease,[6] recurrent venous thrombosis,[7] and hyperbetalipoproteinemia.[8] The mechanism of these changes is not yet fully understood, but sulfinpyrazone inhibits platelet aggregation and the release reaction in vitro,[9–11] decreases platelet coagulant activity,[12] reduces adherence of platelets to subendothelial structures,[13,14] and protects the endothelium from damage.[15] Although conflicting results have emerged with regard to the ability of the drug to inhibit aggregation in vivo at therapeutic regimens,[3,16–18] prolonged competitive and reversible inhibition of arachidonic acid-induced aggregation and prostaglandin synthesis has been reported.[10,19,20]

Platelet hyperaggregability has been reported in coronary artery disease and myocardial infarction by several investigators,[21,22] but the observations were often limited to adenosine diphosphate and collagen. However, we found that patterns of platelet hyperaggregability differ in the various forms of ischemic heart disease, and examples are the selective platelet hyperresponsiveness to thrombin of young patients with myocardial infarction and angiographically normal coronary arteries and the characteristic platelet hypersensitivity to epinephrine of patients with variant angina.[23,24]

Whether the foregoing platelet changes are primarily or secondarily involved in the process of myocardial infarction and coronary vasospasm is still open to question. In the present study, we took advantage of our participation in the Anturane Reinfarction Trial[25] to carry out platelet function tests and to attempt to correlate platelet changes with the clinical issues of the study. A preliminary report was issued previously[26] and complete data are now presented.

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TABLE I Clinical Data

Variable	Patients With Sulfinpyrazone			Patients With Placebo	
Age					
Range (yr)	47–62			45–62	
Mean ± SE	55.6 ± 1.5			53.7 ± 1.3	
Sex					
F	2			3	
M	19			17	
Days (n) post-MI at entry in the study					
Range	28–35			25–35	
Mean ± SE	30.0 ± 0.5			30.1 ± 0.6	
Cigarette smoking	15 (12)			15 (13)	
Hypertension (>150/100 mm Hg)	4			0	
Diabetes mellitus	1			2	
Serum cholesterol (mg/dl)					
Mean ± SE	225 ± 7	(239 ± 9)		238 ± 15	(230 ± 9)
Patients >250	8			9	
Serum triglycerides (mg/dl)					
Mean ± SE	206 ± 17	(220 ± 18)		229 ± 19	(219 ± 16)
Patients > 150	12			10	
Serum uric acid (mg/dl)					
At entry (0)	6.6 ± 3			6.5 ± 3	
After 6 mo	2.9 ± 0.1		$p < 0.001$	6.7 ± 3	
After 12 mo	2.7 ± 0.2		$p < 0.001$	6.3 ± 3	
Patients (n) taking:					
Propranolol	8			13	
Isosorbide dinitrate	3			6	
Hydrochlorothiazide	4			1	
Digoxin	3			2	
Furosemide	2			2	
Diazepam	1			3	
Allopurinol	1			1	
Various other drugs	5			6	
Recorded deaths	1 (MI; 22 mo)			1 (MI; 13 mo)	
Patients withdrawn	0			1 (Hodgkin's)	

Values 1 year after inclusion in the study are given in parentheses. MI = myocardial infarction; SE = standard error of the mean.

Methods

Patients: Of the 107 patients with recent myocardial infarction enrolled in the Anturane Reinfarction Trial at the Montreal Heart Institute, 41 were allocated at random for platelet aggregation and blood follow-up studies. The reader is referred to the description of the multicenter trial[25] for details concerning patient eligibility and procedures. At the end of this double-blind randomized study, 21 patients had received sulfinpyrazone, 200 mg 4 times a day. Of the 20 patients who were given a placebo, 1 was withdrawn from the study after having completed the 1st year, because of Hodgkin's disease.

The clinical data on our patients are summarized in Table I. No difference was observed between the 2 groups with regard to time of enrollment after myocardial infarction, age, sex, smoking habits, serum cholesterol, serum triglycerides, and serum uric acid at the beginning of the study. However, 4 patients in the sulfinpyrazone group had elevated blood pressure. Of the drugs used concomitantly, propranolol was the most commonly prescribed with 8 and 13 patients, respectively, in the sulfinpyrazone and the placebo groups.

Four predetermined laboratory visits were chosen for our study. They corresponded to the time of enrollment before the start of the double-blind medication (indicated as 0 month in illustrations and tables) and to 6, 12, and 24 months after the onset of therapy. Blood was collected between 8:00 and 9:00 A.M. from a forearm vein in syringes containing the appropriate anticoagulant solutions, after a 10 to 12 hour fast including abstinence from drugs and smoking. The samples were drawn at the same time as those for the routine analyses established in the trial, including blood lipids and serum uric acid; these tests were carried out by a central laboratory and the results were not made available to the investigators until completion of the trial. Informed consent was obtained from each subject for the supplementary investigations they underwent in the scope of the present study.

Laboratory investigations: Aggregation of platelets was tested on platelet-rich plasma at each visit, according to methods previously described.[24] Aggregating agents and their final concentrations in the samples were as follows: adenosine diphosphate 0.228, 0.455, and 0.91 μg/ml (Sigma Chemicals, St. Louis); topical bovine thrombin, 0.185 and 0.246 U/ml; adrenaline chloride 0.228, 0.455, and 0.91 μg/ml (Parke-Davis, Detroit) prepared in tyrode-albumin solution; and collagen, 0.228, 0.455, and 0.91 μg/ml dissolved in glacial acetic acid.

The citrated platelet-rich plasma was obtained by centrifugation and the platelet counts were adjusted to $350 \times 10^3/\mu l$. The tests were initiated by the addition of 50 μl of the reagent to 500 μl of platelet-rich plasma on a Payton Dual Channel aggregometer at 37°C. The aggregation response was recorded for more than 3 minutes and the curves were computed on a Hewlett-Packard Calculator 9830A with digitizer, for analysis of the speed of aggregation (maximal slope of the reaction; 1 cm/cm = 10% transmission/0.5 min), extent of aggregation (surface under the curve; 1 cm^2 = 5% transmission-minute), and magnitude of aggregation (maximal amplitude of the curve; 1 cm = 10% transmission). These calculations were performed 1 minute after the addition of thrombin and 1 and 3 minutes after adenosine diphosphate and epinephrine for estimation of the primary and secondary waves of aggregation, and after 3 minutes with collagen.

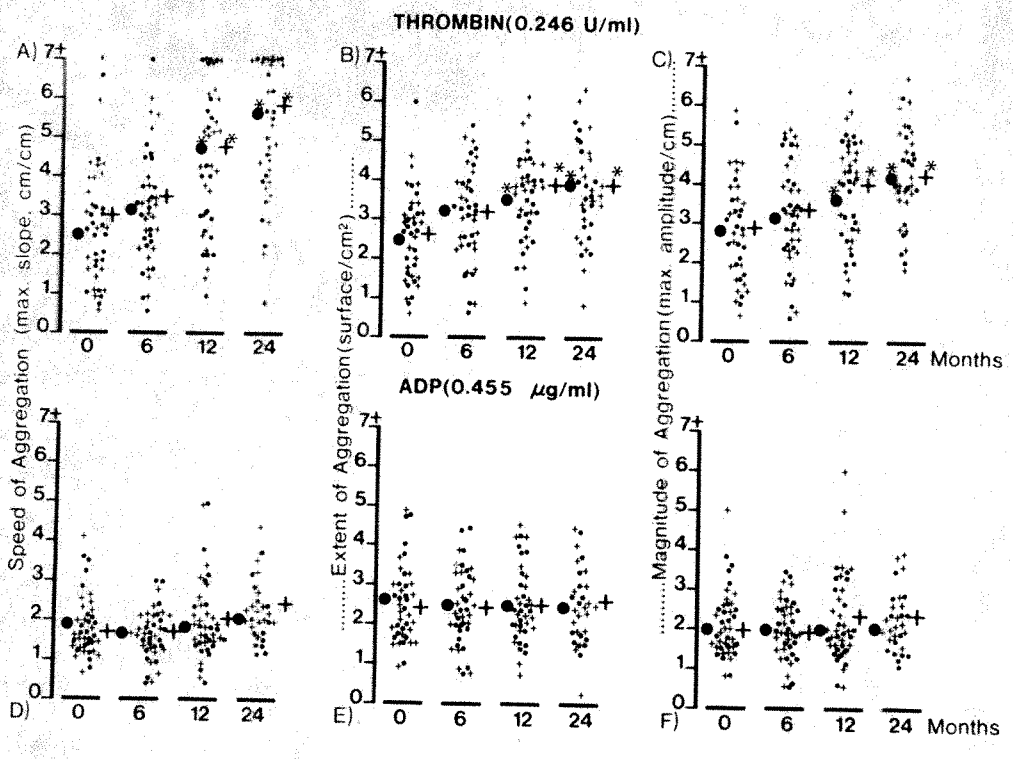

FIGURE 1. Platelet aggregation follow-up data: responses of platelet-rich plasma to thrombin and adenosine diphosphate (ADP). **Large signs** indicate means.

At the last visit after 2 years of treatment, aggregation to thrombin (0.015 and 0.030 U/ml) in the absence or presence of epinephrine (0.55 μg/ml) was also estimated on washed platelet suspensions (350 × 10^3 platelets/μl) prepared from acid-citrate-dextrose anticoagulated blood.[24]

Production of malonyldialdehyde was also estimated after stimulation of the washed platelet suspensions with 2.7, 0.68, and 0.34 U of thrombin/ml ± epinephrine (0.55 μg/ml) according to the method of Smith et al.[27] modified by Zucker.[28] One milliliter of the platelet suspension incubated at 37°C and stirred at 900 rpm was challenged with 100 μl of the aggregant. The reaction was stopped after 3 minutes by the addition of 1.1 ml of trichloroacetic acid. Malonyldialdehyde was estimated after reaction with 2-thiobarbituric acid.[29,30] The results were expressed in nanomoles of malonyldialdehyde/10^9 platelets. Normal reference values were obtained from a group of 20 normal healthy volunteers aged 20 to 48 years (mean 30 years) recruited among the hospital staff.

Platelet coagulant activity and cephalin clotting times were estimated at the first 2 visits according to platelet unactivated and collagen activated systems. As reported previously,[31] a Biodynamics coagulometer coupled to a recording system was used to evaluate the clotting times, as evidenced by changes in optical densities. The basic unactivated test consists in a modification of the plasma recalcification time[32]: 100 μl of platelet-rich plasma (120 × 10^3 platelets/μl) is incubated during 5 minutes at 37°C with 100 μl of tris-buffered saline solution. Saline solution (20 μl) is added and the incubation prolonged for exactly 60 seconds followed by the addition of 100 μl $CaCl_2$, M/50. In the activated system, collagen (20 μg; Sigma Chemicals, St. Louis) homogenized in saline solution is substituted for the 20 μl of saline solution. Assay of the cephalin time is carried out by replacement of platelet-rich plasma by platelet-poor plasma (less than 2 × 10^3 platelets/μl) and of a 1/100 diluted rabbit brain cephalin extract[33] instead of 100 μl of tris-buffered saline solution. Plasma prekallikrein was measured on citrated plasma by use of a 2-stage esterolytic assay described in detail elsewhere.[34]

Statistics: Unless specified, Student's *t* test for comparison of means and a level of significance of 0.05 were used for statistical analysis. In addition, as indicated in the text, the *t* test method for paired comparisons was also utilized.

Results

Clinical data: As shown in Table I, no significant change was observed in serum levels of cholesterol and triglycerides after 1 year, and a similar number of patients stopped smoking in both groups. Two deaths were recorded during the study, 1 in each group, and both followed recurrent myocardial infarction.

As expected, serum uric acid levels were greatly reduced in all patients given sulfinpyrazone, the mean reduction being close to 60% ($p < 0.001$) for the group. Except in 4 cases, 2 in each group, who at one time during the study showed values incompatible with the mode of therapy (levels unchanged with sulfinpyrazone and reduced by 50% with placebo), analysis of the individual serum uric acid patterns showed compliance to the double-blind drug regimens and all the results were included in our final analysis.

Laboratory data: Aggregation (speed, extent, and magnitude) of platelet-rich plasma induced by thrombin was equivalent in the 2 groups throughout the study (Fig. 1). However, the response increased in a gradual

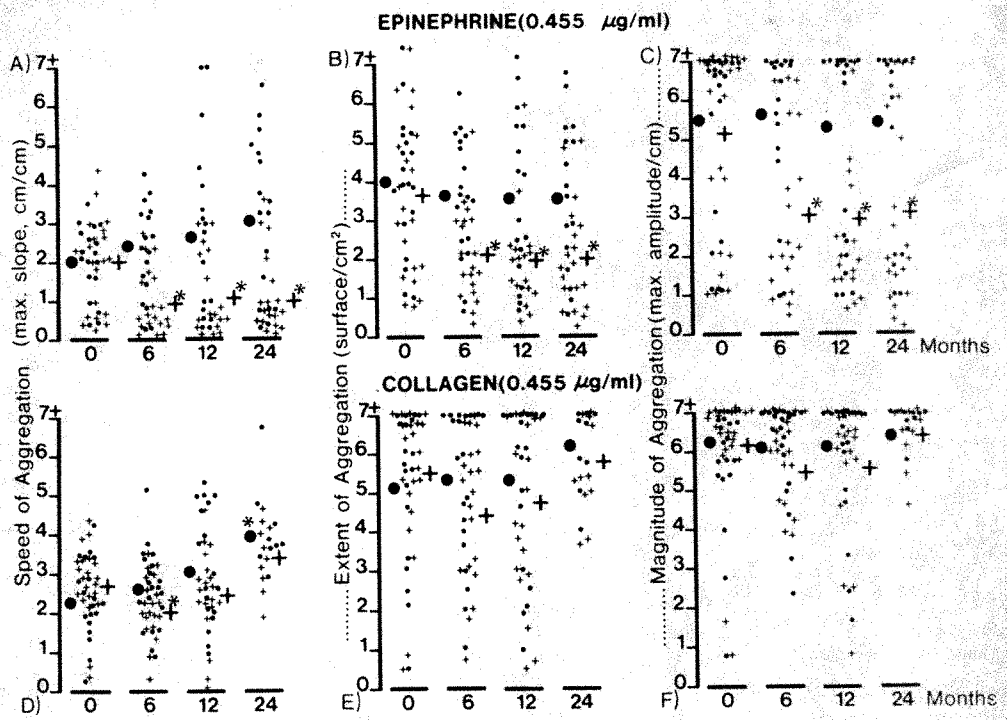

FIGURE 2. Platelet aggregation follow-up data: responses of platelet-rich plasma to epinephrine and collagen. **Large signs** indicate means.

and similar manner in both the placebo and sulfinpyrazone group and the changes reached statistical significance ($p < 0.05$) after 12 and 24 months; the increases were also significant ($p < 0.05$) after 6 months when paired t test comparisons were made. These results contrast with those obtained with adenosine diphosphate. Both groups responded equally to adenosine diphosphate, and no change whatsoever was measured during the study at all the concentrations tested.

The response of platelet-rich plasma to epinephrine and collagen is illustrated in Figure 2. At no time was a measurable change in platelet response to epinephrine observed in the placebo group. In contrast, a 40 to 50% ($p < 0.05$) reduction in the speed, extent, and magnitude of aggregation was noted in the sulfinpyrazone-treated group. The placebo and sulfinpyrazone groups differed statistically at 6, 12, and 24 months. Maximal reduction of aggregation was reached after 6 months and remained constant thereafter. The reduction of aggregation involved mainly the secondary wave of aggregation but also the primary wave. Analysis of aggregation responses 1 minute after addition of epinephrine, a time when the secondary response had not yet taken place, revealed a significant ($p < 0.02$, t test for paired comparisons) reduction from pretherapeutic aggregation responses. Typical epinephrine-induced aggregation curves in a patient with platelet hyperaggregability and treated with sulfinpyrazone are shown in Figure 3.

With regard to collagen, the speed of aggregation slightly increased ($p < 0.05$ after 1 year; paired t test) in the placebo group, but the extent and magnitude of aggregation remained unchanged. However, in the sulfinpyrazone group, aggregation to collagen was mildly decreased. Nevertheless, the 2 groups were statistically similar in their response to collagen aggregation during the entire study.

The aforementioned significant changes in platelet aggregation to thrombin and epinephrine were not related to propranolol therapy. Patients receiving propranolol at the time of their admission to the project had an enhanced aggregation to all reagents tested ($p < 0.02$ for thrombin and adenosine diphosphate) as compared with patients not taking the drug. Despite this, we observed a similar decrease (45%) in aggregation to epi-

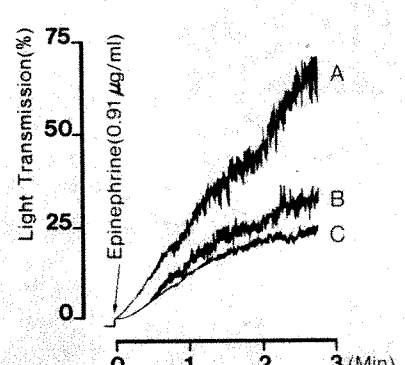

FIGURE 3. Typical aggregation responses of platelet-rich plasma to epinephrine in a patient with hyperaggregability before sulfinpyrazone (A) and after 6 (B), 12, and 24 months (C).

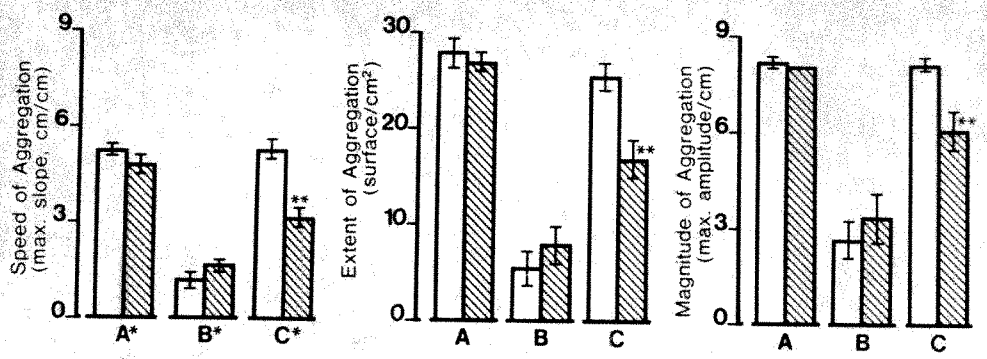

FIGURE 4. Aggregation of washed platelet suspensions by thrombin and its potentiation by epinephrine; effect of sulfinpyrazone.

nephrine and a similar increase (50%) in aggregation to thrombin in subgroups of patients taking sulfinpyrazone alone (n = 13) or in association with propranolol (n = 8). Because of the limited number of patients taking other drugs (Table I), their possible effects could be evaluated only on an individual basis; no detectable effect was observed.

Thrombin (0.03; 0.015 U/ml) elicited similar aggregation responses on washed platelet suspensions from placebo- and sulfinpyrazone-treated groups (Fig. 4). However, in the group receiving sulfinpyrazone, the potentiation effect by epinephrine at a low concentration (0.015 U/ml) of thrombin was about half ($p < 0.01$) that measured in the placebo group. On the other hand, thrombin induced production of malonyldialdehyde in a dose-related manner, from 5.8 nmol/10^9 platelets with 0.34 U/ml of thrombin to 8.6 nmol with 2.7 U/ml, and to the same extent on platelet suspensions from the sulfinpyrazone and placebo patient groups (Fig. 5). Also, the addition of epinephrine (0.55 μg/ml) to a low dose of thrombin (0.34 U/ml) yielded an additional production of malonyldialdehyde (0.48 nmol; $p < 0.05$, *t* test for paired comparisons) that was identical in suspensions prepared from the placebo- and sulfinpyrazone-treated groups. Although the 2 patient groups could not be dissociated from each other in terms of their platelet production of malonyldialdehyde, their response was 30% ($p < 0.01$) greater than that measured in a normal control group under similar conditions.

No significant change was found in platelet coagulant activity after 6 months of therapy in the sulfinpyrazone and placebo groups. As shown in Table II, clotting times of recalcified platelet-rich plasma in the presence or absence of collagen were within the same range in both groups. Activation of the platelets by collagen shortened by 60% the clotting time of platelet-rich plasma in both groups without significant modification of the cephalin clotting time. Neither of the 2 tests discriminated between the 2 groups.

Plasma prekallikrein (Table III) declined gradually but very slightly in the sulfinpyrazone group. The reduction was significant ($p < 0.05$; *t* test for paired comparisons) after 1 and 2 years of therapy. However, the change was so small that the placebo- and sulfinpyrazone-treated groups could not be dissociated from each other on a statistical basis.

Discussion

Ex vivo measurements of platelet aggregation indicate that sulfinpyrazone, 200 mg 4 times a day, does not produce a generalized and sustained inhibition of platelet aggregation in man. Of the 4 aggregating reagents known to interfere with hemostasis in vivo, and used here in vitro at different concentrations to produce

TABLE II Effects of Sulfinpyrazone and Placebo on Platelet Coagulant Activity Tested in Activated and Unactivated Systems

Groups	Time in the Study (mo)	Coagulation Times (s)			
		Without Platelet Activator		With Collagen Activation	
		PRP	PPP	PRP	PPP
Sulfinpyrazone	0 (entry)	685 ± 21	213 ± 9	267 ± 10	216 ± 14
Sulfinpyrazone	6	*747 ± 30	224 ± 10	269 ± 10	216 ± 10
Placebo	0	645 ± 26	223 ± 9	272 ± 10	213 ± 11
Placebo	6	*708 ± 30	231 ± 11	258 ± 10	211 ± 6

Results are given as mean ± standard error of the mean.
* $p < 0.05$ versus values at 0 (paired *t* test analysis).
PPP = platelet-poor plasma; PRP = platelet-rich plasma.

minimal to maximal aggregation, only the response to epinephrine was significantly modified by sulfinpyrazone as compared with placebo.

The observed reduction (50%) in epinephrine-induced aggregation can be interpreted as a normalizing effect of sulfinpyrazone therapy on platelet sensitivity to catecholamines rather than as a specific inhibition of aggregation, and can be compared with the reported prolongation of platelet survival time produced by the drug in several clinical states.[2–7] An initial observation supporting this hypothesis is that complete inhibition of the epinephrine response was not encountered in any of our patients and that the mean response elicited by epinephrine in patients receiving sulfinpyrazone was identical to that previously reported in untreated normal volunteers, using the same methods.[24] Therefore, it appears that sulfinpyrazone simply corrected the hyperreactivity of platelets to epinephrine which was present in both groups at the start of the study and remained unchanged thereafter in the placebo group.

A second argument favoring the idea of a normalization process is that the washed platelet suspensions obtained from the sulfinpyrazone-treated patients were much less sensitive to the potentiating effect of epinephrine on a low concentration of thrombin, although inhibition of aggregation by sulfinpyrazone is cleared by reversible and competitive[10] and the washing process for preparation of platelet suspensions.[35] An additional indication derives from the observation that although reduction of the epinephrine response primarily involved the secondary wave aggregation, the primary wave was nonetheless significantly attenuated by sulfinpyrazone therapy. It is generally accepted that the primary wave of aggregation induced by epinephrine is mediated by stimulation of the alpha-adrenergic receptors and prevented by alpha-adrenergic blocking agents,[36] whereas secondary aggregation results from the release of platelet constituents, mainly endoperoxides and thromboxane A_2.[37] However, a similar production of malonyldialdehyde was measured after the addition of epinephrine and thrombin to platelet suspensions from both the sulfinpyrazone and placebo groups, indicating that inhibition of prostaglandin synthesis was not involved in the observed reduction of platelet aggregation to epinephrine in our sulfinpyrazone-treated patients. This result differs from those reported with arachidonic acid-induced aggregation.[19,20] Therefore, another mechanism must also be involved; it is unlikely to be another factor in the release reaction because no significant inhibition was measured with low concentrations of thrombin and collagen in the sulfinpyrazone group.

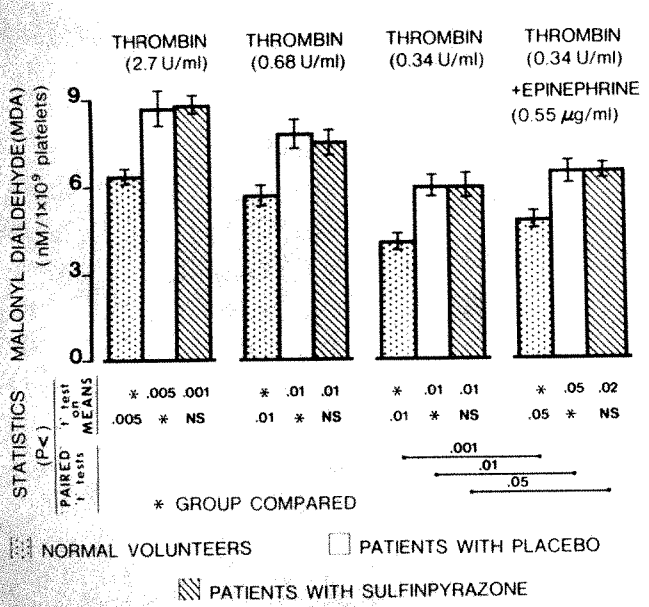

FIGURE 5. Malonyldialdehyde production by washed platelet suspensions stimulated with thrombin and thrombin + epinephrine.

TABLE III Effect of Sulfinpyrazone Therapy on Plasma Prekallikrein

Groups	Prekallikrein (μM, TAME Hydrolyzed/h/ml plasma) 0 (entry)	6 mo	12 mo	24 mo
Sulfinpyrazone	112.1 ± 3.1	107.4 ± 2.7	103.3 ± 3.7*	105.7 ± 4.4*
Placebo	112.2 ± 4.4	110.1 ± 3.1	109.3 ± 3.7	109.6 ± 3.7

* $p < 0.05$ versus values at entry in the project (paired t test analysis).

Additional evidence that normalization rather than inhibition of the platelet response to epinephrine may have taken place can be drawn from the observation that platelet aggregation to epinephrine in man is not modified 2 hours after administration of a single dose of sulfinpyrazone nor after 4 days of treatment as in the present study.[16] Therefore, our observation made after 6 months of sulfinpyrazone therapy and 10 hours after the last intake of the drug is apparently the result of sustained and long-term treatment.

Platelet aggregation induced by thrombin in platelet-rich plasma was far greater than normal[24] at the onset of the study and kept increasing gradually in the following 2 years in both groups of patients. Increased aggregation to thrombin has been associated with a higher risk of thrombosis[38] and myocardial infarction[24], and the observed failure of sulfinpyrazone to control the hyperaggregability to thrombin in our patients is possibly related to the reported ineffectiveness of the drug in preventing recurrence of myocardial infarction in the Anturane Reinfarction Trial.[25] However, the platelet hyperresponsiveness to thrombin in our patients was not the result of intrinsic platelet changes as we previously reported in young patients with myocardial infarction and normal coronary arteriograms,[24] but rather was due to plasma environmental changes as indicated by the normal response of the washed platelet suspensions to thrombin.

In accordance with Cortellaro et al.[39] we found no significant difference between the placebo and sulfinpyrazone groups in platelet response to adenosine di-

phosphate. However, a slight decrease was seen in response to collagen in the sulfinpyrazone group, suggesting a weak effect of the drug. However, the 2 groups of patients remained identical on a statistical basis. Release or availability of platelet coagulant material (Table II) and plasma prekallikrein (Table III) was not modified by the sulfinpyrazone regimen. This last observation contrasts with the results reported in patients with myocardial infarction and normal coronary arteriograms in whom high levels of prekallikrein were found in association with their tendency to coronary spasm.[24]

The association of propranolol with sulfinpyrazone had no influence on the platelet aggregation response to epinephrine and thrombin. However, when all the patients taking propranolol before the start of the drug trial were, as a group, compared with those not taking the beta-blocking drugs, we found significant ($p < 0.02$) increases in platelet aggregation, particularly to thrombin and adenosine diphosphate. To explain such a result one may question the severity of the disease or the associated factors requiring beta-blockade therapy, but as we previously reported, blockade of the beta-receptors enhances slightly the aggregation of human platelets and strongly those of other species.[36]

In conclusion, normalization or reduction in the platelet response to epinephrine is the only significant observation that distinguished the sulfinpyrazone and placebo groups in this study. This change in platelet response to epinephrine in relation to the reported benefit of the drug in reducing the rate of sudden death after myocardial infarction remains speculative. However, the observation may also indicate an important drug or disease process taking place elsewhere in the organism, with no particular or restrictive relevance to platelets and platelet aggregation. As a matter of fact, sulfinpyrazone has been shown to act on cell membrane, to inhibit in high dosages, like alpha-adrenergic blocking agents, the primary wave of platelet aggregation induced by epinephrine in vitro,[11] to protect the endothelium from damage,[15] and to prevent arrhythmias in isolated rabbit heart preparations.[40]

Acknowledgment

We sincerely thank Marie-Andrée Séguin, study coordinator of the Anturane Reinfarction Trial at the Montreal Heart Institute, for her dedication and spontaneous collaboration in the study, Pierre Meloche for his technical assistance, and Suzanne Morin for her secretarial work.

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Familial Aggregation of Coronary Heart Disease and Its Relation to Known Genetic Risk Factors

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The question of how much of the familial aggregation of coronary heart disease is explained by familial clustering of coronary risk factors was approached by a case-control study involving 145 white male survivors of myocardial infarction, 145 age-matched white male blood donors, and the first-degree relatives of both groups. Certain risk factors such as serum cholesterol, triglyceride, and fasting blood glucose levels, blood pressure, and smoking history were determined in patients and control subjects. Relatives were interviewed. If the person was deceased, a copy of the death certificate was obtained. With the exception of high blood pressure, risk factors were significantly more frequent in patients than in control subjects.

Among first-degree relatives of survivors of myocardial infarction, 16% had had a myocardial infarction, compared with 8.9% of relatives of control subjects. The frequency of coronary heart disease among first-degree relatives of patients and control subjects was 20.5 and 14.7%, respectively. To find out whether this higher frequency among relatives of patients was fully explained by the existence of known genetic risk factors among survivors of myocardial infarction, 2 approaches were taken. First, statistical analysis that eliminated the role of the various known genetic risk factors (by data stratification according to confounding risk variables and subsequent calculation of a pooled relative risk estimate according to the Mantel-Haenzel method) still indicated an approximately 2-fold (2.14) relative risk for myocardial infarction among families of survivors of myocardial infarction (and a risk of 1.71 for coronary heart disease). Similarly, another approach (Cox's life table regression analysis) confirmed that the classic risk factors could not predict familial occurrence.

These results indicate that the *familial aggregation of coronary heart disease is not entirely explained by the familial clustering of currently known coronary risk factors.* Such familial aggregation could be caused by yet undefined genetic factors, by environmental factors common to family members, or by interaction of genetic factors with environmental agents.

Coronary heart disease and myocardial infarction tend to run in families. In case-control studies the incidence of myocardial infarction in first-degree relatives of patients with myocardial infarction is about 2 to 4 times higher than among first-degree relatives of healthy control subjects.[1-9] The risk for relatives of younger victims of myocardial infarction is higher than for relatives of older patients, although this was not seen in 1 study.[2,6,10] Concordance rates are higher in monozygotic than in dizygotic twins.[11-13] Heritability estimates range from 20 ± 10%[8] to as high as 80%.[14]

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Clinical and prospective cohort studies have revealed several variables that predict coronary heart disease and myocardial infarction. Although the causal relations of these variables in coronary heart disease are not yet completely clear, they are generally referred to as risk factors. Well-known major risk factors include smoking, high blood pressure, hyperlipidemia, and diabetes. Some risk factors such as hypertension, hyperlipidemia, and diabetes mellitus clearly have an important genetic component. Clear Mendelian patterns of familial occurrence of coronary heart disease are occasionally observed. The most frequently implicated major gene is that for familial hypercholesterolemia, with a population frequency of 0.1 to 0.5%.[15] However, most instances of familial aggregation of coronary heart disease and myocardial infarction do not conform to monogenic inheritance.

The question arises whether the familial aggregation of coronary heart disease can be fully explained by the presence of currently known major genetic risk factors such as hypertension, hyperlipidemia, and diabetes. The present study provides evidence for familial aggregation apart from that contributed by these risk factors.

Methods

Selection of probands: interview procedures and examinations: Medical records of persons admitted to 5 hospitals in the Seattle area in the years 1974 and 1975 were reviewed to ascertain all male, Caucasian, 30 to 59 year old survivors of myocardial infarction. Criteria for acceptance of the diagnosis were identical to those used in an earlier study.[16] Of the 198 patients identified, 145 were available for our study (see later for reasons of exclusion). The accessible patients were contacted by phone by a field worker. Information was asked about the patient's present health status; his past medical examination, diet, and drug history; his smoking habits; the family structure; and the names and phone numbers of his first-degree relatives and their willingness to cooperate in the study.

Voluntary blood bank donors from the Puget Sound Blood Center in the years 1977 and 1978 were invited to participate in a study of familial chronic disease until 145 male Caucasian control subjects age-matched with the 145 patients had been found. No mention was made of our interest in heart disease. The policy of the Blood Center was to exclude from donations diabetic patients on insulin treatment, epileptic patients and persons taking beta blocking agents or antibiotic drugs (except for acne treatment), as well as those with a blood pressure exceeding 180/100 mm Hg (after rest). Other reasons for exclusion from the study were a history of hepatitis or any known contact with hepatitis, and work with blood or blood products. Medical personnel, persons with blood disorders, ill persons, and those who had undergone major surgery in the last 6 months were also excluded. Persons taking oral antidiabetic, antihypertensive, antidiuretic, or antihyperlipidemic agents were *not* excluded.

The 145 control subjects were contacted by phone by a field worker and were presented the same questions posed to the patients. All 145 patients and 145 control subjects were examined for blood pressure, pulse rate, fasting serum cholesterol, serum triglyceride, blood glucose levels, and urinary protein and sugar.

All parents and siblings who could be reached by phone and were willing to answer our questions were interviewed in the same way as the survivors of myocardial infarction and control subjects. Relatives who were deceased, had no phone, or were otherwise unable or unwilling to cooperate were not excluded from the study, but information on their medical history was obtained either from the index case or from another relative, or by mailing a questionnaire to those without phones. If a person was deceased, every effort was made to obtain a copy of his or her death certificate. Because the ages of the relatives play an important role in the analysis, relatives, either living or dead, whose ages were not precisely known were excluded from the study. Because information on the relatives below age 30 years had not been collected consistently, this age category was excluded also. The family members were not examined.

Description of probands and families: Of the 198 survivors of myocardial infarction, 145 were available for the study. The other 53 (27%) were excluded for the following reasons: 25 refused, 12 had died after discharge from the hospital, in 9 cases the attending physician did not grant permission, 4. were not in the Seattle area by the time of the study, and 3 had acquired another serious disease. To rule out any bias as a result of these exclusions, we compared in detail the hospital records of the 145 patients who did with the 53 patients who did not participate in the study. No evidence of significant differences could be found.

Figure 1 shows the age distributions of the patients and control subjects at the time of interview. The close resemblance of both distributions—caused by the age-matching—is obvious.

Table I gives the number of relatives of the patients and control subjects. Numbers without parentheses refer to relatives whose ages were exactly known and above 29 years; numbers in parentheses include also the relatives below age 30 years or with age unknown who were omitted from further analyses (23 relatives of patients and 33 relatives of control subjects). The mean number of siblings, 2.53 (2.57) and 2.31 (2.40), of patients and control subjects, respectively, did not differ significantly; neither did the sex ratios in both groups of siblings.

Table II shows the number of relatives with and without interviews, the number of dead and living relatives among those without interview, and the number of those with and without death certificate information among the deceased persons. There are no statistically significant differences between relatives of patients and relatives of control subjects in source and completeness of information, nor with respect to the proportion of relatives living or dead.

Figure 2 shows the age distributions of the relatives of both groups of probands. On the average, relatives of patients were 2 years younger than relatives of control subjects (mean age ± standard deviation for relatives of patients [58.99 ± 12.95] and for relatives of control subjects [61.03 ± 13.98]). The difference was statistically significant (Mann-Whitney U test; $p < 0.01$). An even larger difference (4 years) was found for the age at death of those deceased (62.07 ± 13.17 for relatives of

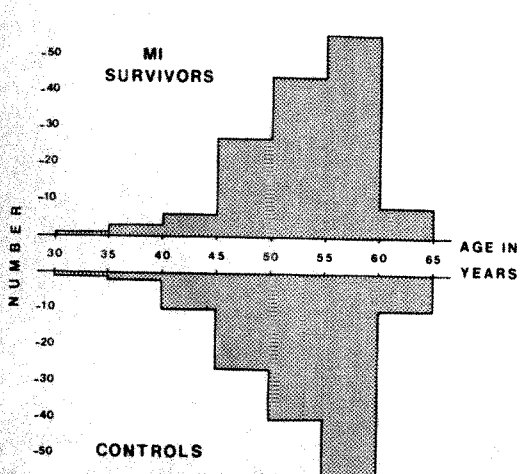

FIGURE 1. Age distributions of patients (survivors of myocardial infarction [MI]) and control subjects.

TABLE I Number of Parents and Siblings of Patients and Control Subjects*

Family Relationship	Number of Relatives of Patients	Number of Relatives of Control Subjects
Father	136 (145)	133 (145)
Mother	136 (145)	137 (145)
Brother	185 (188)	153 (162)
Sister	182 (184)	182 (186)
Total	639 (662)	605 (638)

* Numbers without parentheses refer to relatives whose ages were known exactly and above 29 years; numbers in parentheses also include the relatives below 30 years of age and those with age unknown who were not included in further analysis.

TABLE II Source of Information in Parents and Siblings of Patients and Control Subjects

Source of Information on Relative	Number and Percentage of Relatives of: Patients n	Patients %	Control Subjects n	Control Subjects %
Interview	347	54.3	347	57.4
No interview	292	45.7	258	42.6
Relative deceased	230	36.0	202	33.4
With death certificate	196	30.7	180	29.8
Without death certificate	34	5.3	22	3.6
Other reasons	62	9.7	56	9.3
Total	639	100	605	100

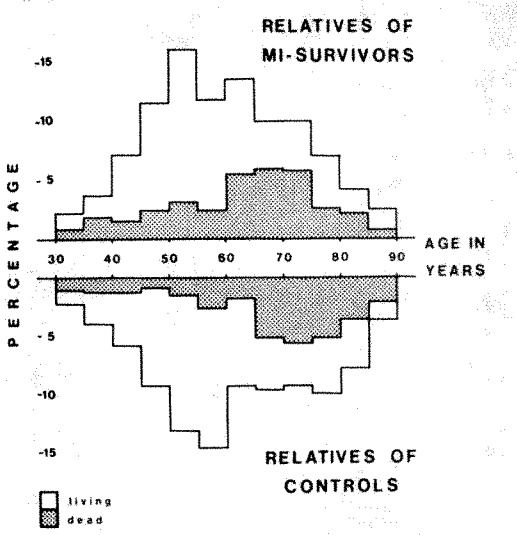

FIGURE 2. Age distributions of first-degree relatives of patients (survivors of myocardial infarction [MI]) and control subjects.

patients and 66.45 ± 14.50 for relatives of control subjects; $p < 0.01$). Presumably this finding was related to frequent and earlier death from coronary heart disease in the relatives of the survivors of myocardial infarction.

The average age of living relatives (57.20 ± 12.51 for relatives of patients and 58.31 ± 12.90 for relatives of control subjects) did not significantly differ for the 2 groups. As expected, the age at death of those deceased was significantly higher than the age of those living, both in relatives of patients and in relatives of control subjects ($p < 0.001$). Because the risk of coronary heart disease increases with age, the analysis of the occurrence of coronary heart disease among the relatives of patients and control subjects has to consider these age differences.

Methods of analysis: Confounding variables such as sex, age, and other risk factors have to be controlled for a meaningful comparison of the prevalence of coronary heart disease in relatives of patients and relatives of control subjects. In the present study this was done in 2 ways.

First, the data were stratified according to the confounding variables. This procedure resulted in a large number of tables with the numbers of relatives of patients and the relatives of control subjects with and without myocardial infarction or coronary heart disease. Within each table, apart from the family history, persons resemble each other with respect to risk factors. For each table the relative risk for developing myocardial infarction or coronary heart disease, depending on the type of family to which a person belongs (patient family or control family), was calculated. The relative risk estimates of these tables were then pooled by the Mantel-Haenzel method and tested for heterogeneity with Woolf's method.[17] This procedure resulted in a *pooled relative risk estimate* for developing myocardial infarction or coronary heart disease.

Stratification of the data results in numerous tables because of the number of risk factors. Many of these tables include few or no persons at all. To reduce the number of tables we used a cumulative risk score (Framingham cardiovascular risk coefficient[18]) instead of separate risk factors. This risk coefficient is obtained by multiplying the value of several risk variables by a coefficient for that variable, summing these products, and adding an intercept. Risk factors included are age, age squared, serum cholesterol, systolic blood pressure, cigarette smoking (yes or no), left ventricular hypertrophy (yes or no), glucose intolerance (yes or no), and cholesterol × age.

Because we desired to control for the effect of risk factors with a significant genetic component, we restricted ourselves to the inclusion of serum cholesterol, blood pressure, glucose tolerance and cholesterol × age in our risk score, using the

TABLE III Prevalence of Coronary Heart Disease Risk Factors Reported by Patients and Control Subjects*

Reported Risk Factors	Patients n	Patients %	Control Subjects n	Control Subjects %	Significance†
Elevated blood lipids	49	33.8	17	11.7	‡
Dieting for this problem	46	31.7	13	9.0	‡
Receiving drugs for this problem	10	6.9	1	0.7	§
High blood pressure	54	37.2	22	15.2	‡
Dieting for this problem	24	16.6	7	4.8	‖
Receiving drugs for this problem	31	21.4	13	9.0	‖
Diabetes mellitus	11	7.6	0	0	‖
Dieting for this problem	10	6.9	0	0	‖
Insulin for this problem	3	2.1	0	0	...
Oral antidiabetic therapy	3	2.1	0	0	...
Cigarette smokers	129	89.0	96	66.2	‡

* Because more than 1 risk factor may be reported the total of the columns exceeds the number of probands. † Significance of comparing prevalence of reported risk factors in survivors of myocardial infarction and control subjects. ‡ $0.001 > p$. § $0.05 > p \geq 0.01$. ‖ $0.01 > p \geq 0.001$.

Framingham coefficients for these variables.[18] For instance, the value of our *restricted* risk score for a man aged 45 years with a serum cholesterol level of 200 mg/100 ml, a systolic blood pressure of 150 mm Hg, and no evidence of glucose intolerance will be 0.0258102 × 200 (serum cholesterol) + 0.0156953 × 150 (systolic blood pressure) + 0.6020336 × 0 (glucose tolerance) − 0.0003619 × 200 × 45 (serum cholesterol × age) − 19.770956 (intercept) = −15.51176. Less restricted risk scores, such as scores with inclusion of smoking behavior or smoking behavior and age, were also constructed and used in the analysis.

In the second approach, the *age* at which a relative had a myocardial infarction was analyzed. For this approach the methodology of *life table and survival analysis* was used. In the usual life table method attention is focused on the age at death due to a certain condition. In our analysis we focused

on the age at which myocardial infarction occurred irrespective of death or survival. In the usual life table method "censored" persons are *those who did not die* from the disorder under study until the time of "censoring" (death from other causes, lost to follow-up study, end of study). In our analysis "censored" persons are *those who did not have a myocardial infarction* until the time of "censoring."

The standard life table method allows construction of "survival" curves and comparison of such curves.[19] In this way subsets of the data may be compared 1 by 1 (such as relatives of patients versus relatives of control subjects, males versus females, high risk families versus low risk families). However, a more powerful method is Cox's life table regression model.[20] In this model "censored" survival is considered a function of

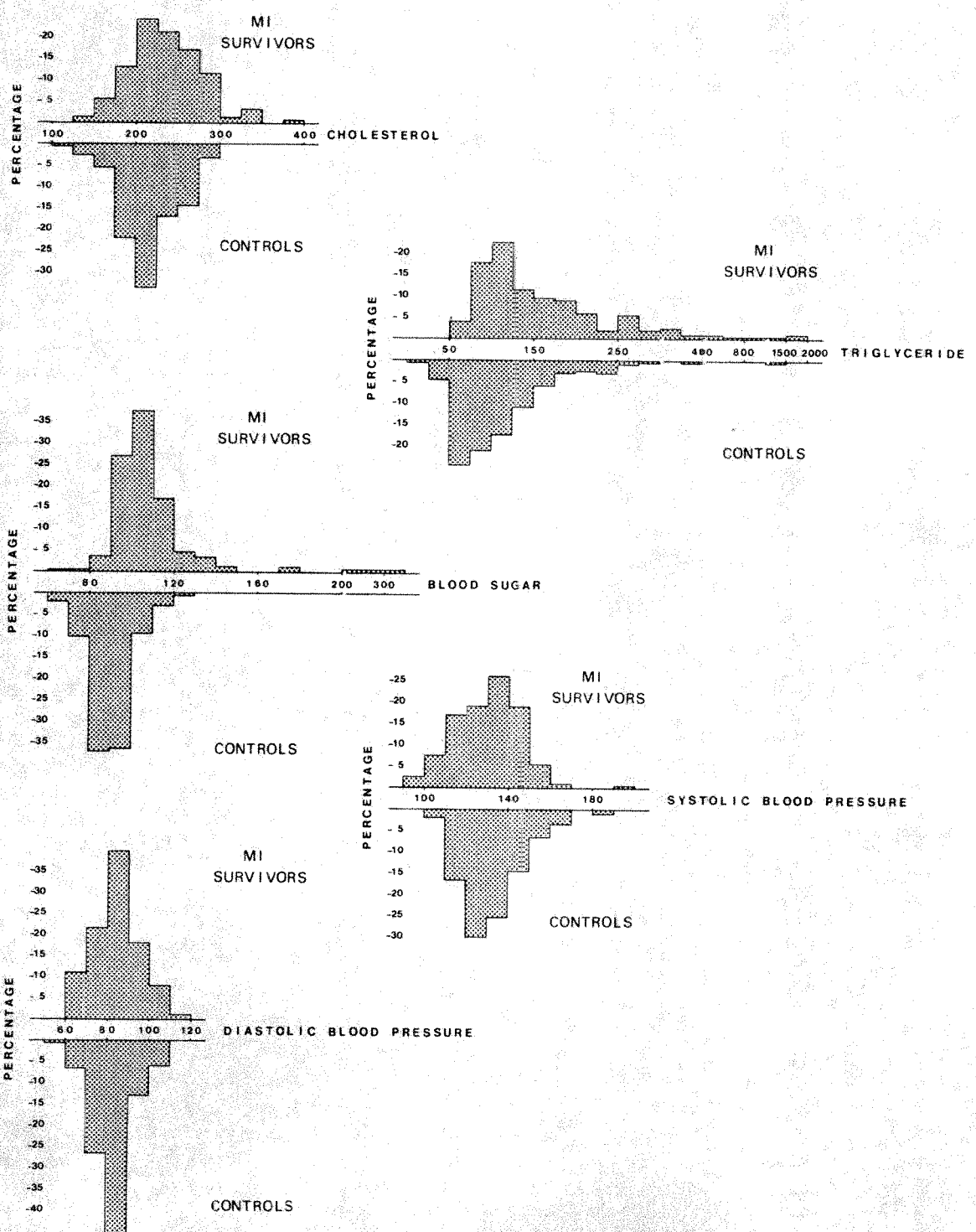

FIGURE 3. Distributions of serum cholesterol, serum triglyceride, fasting blood glucose (mg/100 ml), systolic and diastolic blood pressure (mm Hg) in patients (survivors of myocardial infarction [MI]) and control subjects.

several explanatory variables and unknown regression coefficients multiplied by an arbitrary and unknown function of time. As in classic multiple regression analysis, the model allows simultaneous inferences about the importance of the individual explanatory variables and the unknown regression coefficients.

Throughout this paper p values of 0.05 or greater are regarded as insignificant.

Results

Risk factors in patients and control subjects: Table III shows the reported prevalence of coronary heart disease in patients and control subjects. Figure 3 shows the distributions of serum cholesterol, triglycerides, fasting blood sugar, and systolic and diastolic blood pressure measured in these subjects. The reported prevalence (Table III) of hyperlipidemia, high blood pressure, diabetes mellitus, and cigarette smoking were significantly higher in patients than in control subjects. Correspondingly, the mean serum cholesterol, triglyceride, and blood sugar values in patients were significantly higher than in control subjects (Mann-Whitney U test, $p < 0.001$). However, measured blood pressure, systolic as well as diastolic, was not significantly different in both groups of probands.

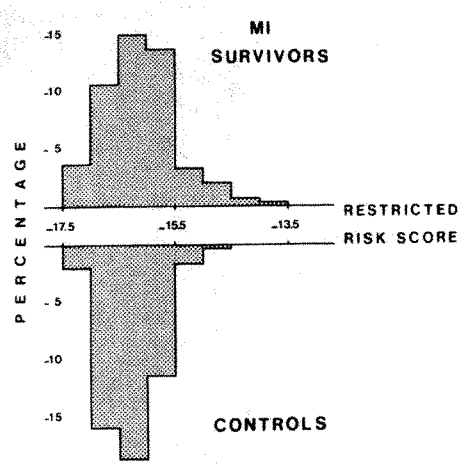

FIGURE 4. Distributions of restricted cumulative risk scores in patients (survivors of myocardial infarction [MI]) and control subjects.

Figure 4 shows the distributions of the restricted cumulative risk scores (see Methods) calculated from serum cholesterol, blood pressure, and glucose tolerance in patients and control subjects. The restricted risk score among patients (-16.10 ± 0.64) was significantly higher than the restricted risk score in control subjects (-16.29 ± 0.44) (Mann-Whitney U test; $p < 0.01$). This also held true when smoking behavior or smoking behavior and age of the proband were included in the computation of the risk score. If the probands were classified according to whether or not they received treatment for hyperlipidemia or hypertension, or both, the risk coefficients were always lowest in control subjects not receiving such treatment. Risk coefficients in these probands generally differed significantly from the risk coefficients in all other groups.

Risk factors in relatives: Table IV compares the reported prevalence of coronary heart disease risk factors in the first-degree relatives of patients and control subjects. Contrary to the findings in the patients and control subjects (Table III), the relatives of patients did not differ significantly from the relatives of control subjects in the reported prevalence of risk factors. However, diabetes and cigarette smoking appear significantly more common among relatives of patients and control subjects with that risk factor than among relatives of those without that risk factor.

A history of high blood lipids or high blood pressure, or both, was not significantly more common among relatives of patients and control subjects with such findings than among relatives of those without such findings. Similarly, high blood lipids and high blood pressure were not significantly more common in relatives of patients and control subjects with serum cholesterol, triglyceride, or systolic or diastolic blood pressure in the upper decile than in relatives of the other patients and control subjects (not shown).

Coronary heart disease in first-degree relatives: Myocardial infarction was reported in 104 (16.3%) of the 639 relatives of patients and in 54 (8.9%) of the 605 relatives of control subjects (Table V). Coronary heart

TABLE IV Prevalence of Coronary Heart Disease Risk Factors Reported in Relatives of Patients and Relatives of Control Subjects

	Percentage of Relatives With Risk Factor Reportedly Present					
	Relatives of Patients			Relatives of Control Subjects		
Reported Risk Factor	Risk Factor Present in Patient	Risk Factor Absent in Patient	Significance*	Risk Factor Present in Control Subject	Risk Factor Absent in Control Subject	Significance†
Elevated blood lipids	9.5	8.3	. . .	16.4	89.3	. . .
High blood pressure	24.7	21.1	. . .	17.9	20.9	. . .
Diabetes mellitus	23.1	5.7	§	. . .	7.8	. . .
Cigarette smoking	51.7	28.9	§	55.7	40.3	‡

* Significance of comparing prevalence of reported risk factors in relatives of *patients* with and without that risk factor. † Significance of comparing prevalence of reported risk factors in relatives of *control* subjects with and without that risk factor. ‡ $0.01 > p \geq 0.001$. § $0.001 > p$.

TABLE V Prevalence of Myocardial Infarction or Coronary Heart Disease in First-Degree Relatives of Patients and Control Subjects

Description of Relatives	Percentage of Relatives With: Myocardial Infarction — Relatives of Patients	Myocardial Infarction — Relatives of Control Subjects	Myocardial Infarction — Significance*	Coronary Heart Disease — Relatives of Patients	Coronary Heart Disease — Relatives of Control Subjects	Coronary Heart Disease — Significance†
All relatives	16.3	8.9	¶	20.5	14.7	‖
Parents	27.2	15.6	‖	34.9	27.0	. . .
Siblings	8.2	3.6	§	9.8	4.8	§
Males	20.6	14.3	. . .	25.2	23.4	. . .
Females	11.9	4.1	¶	15.7	6.9	‖
Age (yr)						
30–52	7.4	3.4	. . .	9.3	3.4	§
53–66	17.3	6.9	‖	19.8	10.8	§
67–88	25.1	15.1	§	34.2	27.1	. . .
Tertile of RRS‡						
Lowest	19.9	8.8	‖	25.7	15.9	§
Middle	17.0	7.9	‖	20.6	12.5	§
Highest	13.5	10.7	. . .	17.2	16.0	. . .

* Significance of comparing prevalence of myocardial infarction in relatives of patients and control subjects. † Significance of comparing prevalence of coronary heart disease in relatives of patients and control subjects. ‡ RRS = restricted cumulative risk score calculated from serum cholesterol, blood pressure, and glucose intolerance (see Methods). § $0.05 > p \geq 0.01$. ‖ $0.01 > p \geq 0.001$. ¶ $0.001 > p$.

disease was reported in 131 (20.5%) of the relatives of patients and in 89 (14.7%) of the relatives of control subjects. Coronary heart disease and myocardial infarction therefore were significantly more prevalent in the relatives of patients than in the relatives of control subjects. Table V also shows the percentages of relatives of patients and control subjects with coronary heart disease and myocardial infarction according to their family relationship (parents or siblings), sex (male or female), age category (30 to 52 years, 53 to 66 years, and 67 to 88 years), and level of restricted cumulative risk score (tertiles). Both coronary heart disease and myocardial infarction were always more prevalent among relatives of patients, although the difference was not significant in every subgroup. As expected, the prevalence of coronary heart disease and myocardial infarction was greater in patients than in siblings, greater in men than in women, and increased with advancing age. Unexpectedly, the prevalence of coronary heart disease and myocardial infarction occurring in relatives did not correlate positively with the restricted cumulative risk score in the patient or control subject, but instead showed an opposite trend, at least in the relatives of patients.

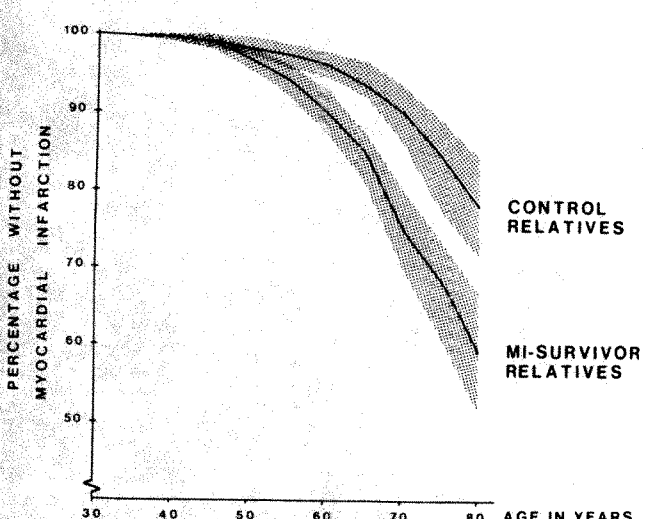

FIGURE 5. Calculated proportions of relatives of patients (survivors of myocardial infarction [MI]) and control subjects without myocardial infarction at reaching ages 30 through 80 years (means with 95% confidence intervals). Calculation according to standard life table method.[19]

Figure 5 shows the calculated proportions of relatives without myocardial infarction on reaching ages 30 through 80 years (standard life table method[19]). When the precise age at their first myocardial infarction was not known (in 58.7% of the relatives of patients and 42.6% of the relatives of control subjects), we used the age at death (77 patients) or "censoring" for other reasons (7 patients). This may have caused some shifting of both curves toward later myocardial infarctions, presumably more so in the patient families (because of the larger number of persons whose age at first myocardial infarction was not known exactly) than in control families. Therefore, the already clear-cut distinction between relatives of patients and relatives of control subjects, shown in Figure 5, may underestimate the real difference.

Relative risk analysis: Data stratification according to type of family (patient or control subject), level of the restricted cumulative risk score in patients or control subjects, age and sex of the relatives, and presence or absence of myocardial infarction than coronary heart disease in these relatives is shown in Table VI. The

TABLE VI Data Stratification According to Type of Family (Patient or Control), Height of the Restricted Cumulative Risk Score (RRS)* in Patient or Control Subject, Age and Sex of the Relatives, and Presence or Absence of Myocardial Infarction (MI) or Coronary Heart Disease (CHD) in These Relatives

Tertile of RRS in Patient or Control Subject	Sex of Relative	Age of Relative (yr)	Relatives (n)							
			Patients				Control Subjects			
			With		Without		With		Without	
			MI	(CHD)	MI	(CHD)	MI	(CHD)	MI	(CHD)
First	M	30–52	3	(3)	22	(22)	1	(2)	22	(21)
		53–66	13	(13)	24	(24)	6	(7)	34	(33)
		67–88	8	(13)	21	(16)	9	(19)	32	(22)
	F	30–52	0	(0)	18	(18)	0	(0)	40	(40)
		53–66	2	(3)	27	(26)	0	(2)	52	(50)
		67–88	8	(12)	25	(21)	5	(8)	38	(35)
Second	M	30–52	5	(7)	38	(36)	3	(3)	38	(38)
		53–66	10	(11)	22	(21)	4	(5)	30	(29)
		67–88	5	(8)	15	(12)	7	(13)	29	(23)
	F	30–52	0	(0)	36	(36)	0	(0)	34	(34)
		53–66	6	(7)	26	(25)	0	(0)	24	(24)
		67–88	7	(7)	24	(24)	3	(6)	44	(41)
Third	M	30–52	8	(8)	50	(50)	2	(2)	26	(26)
		53–66	8	(10)	41	(39)	3	(5)	16	(14)
		67–88	6	(8)	22	(20)	6	(11)	18	(13)
	F	30–52	2	(4)	57	(55)	0	(0)	29	(29)
		53–66	4	(5)	44	(43)	5	(6)	25	(24)
		67–88	9	(12)	23	(20)	0	(0)	20	(20)

* See Methods.

relative risk analysis of these data (Table VII) shows that first-degree relatives of patients have somewhat over twice the risk of having myocardial infarction than first-degree relatives of control subjects, and about 1.7 times the risk of having coronary heart disease. Separate analyses of relatives of patients and control subjects with low risk factors (lipids, blood pressure, and blood sugar) or with low restricted cumulative risk scores show the same results as do analyses with subcategorization of the data according to presence or absence of treatment (either drug or diet) in the patients and control subjects. Similarly, using quartiles instead of tertiles, combining tables with zero observations in 1 or 2 boxes with other tables in several ways, and including smoking behavior or smoking behavior and age in the restricted cumulative risk score all give the same result: myocardial infarction is twice as common in the relatives of patients, irrespective of risk factors in the probands.

Cox's life table regression analysis: Table VIII shows the result of a typical run of the Cox's life table regression analysis. A large number of such analyses have been done, differing among each other in the number and nature of independent variables (risk factors) that were included. Consistent features were the significant positive effect of belonging to a patient family and of male sex, and the absence of any significant effect of the restricted cumulative risk score in patients or control subjects. The presence of drug treatment in patient or control subjects seemed to have some predictive value. Assignment of all the patients and control subjects with drug treatment to the upper tertile of the restricted cumulative risk score did not

TABLE VII Results of the Relative Risk Analysis.*

Disease	Pooled Relative Risk Estimate (R)	Test on R = 1			Test on Homogeneity		
		Chi-Square	df	p	Chi-Square	df	p
Myocardial infarction	2.14	16.463	1	<0.001	19.822	17	0.283
Coronary heart disease	1.71	10.607	1	0.001	26.826	17	0.061

* Data of 18 tables, each containing numbers of relatives of patients and control subjects with and without the disease under study, and differing among each other in risk levels (see Table VI) were pooled according to the Mantel-Haenzel method to obtain a pooled relative risk estimate. Pooling seems justified because no significant heterogeneity was apparent among the 18 tables. The pooled relative risk estimates obtained differ significantly from the null hypothesis of equal risk (R = 1).

TABLE VIII Results of Cox's Life Table Regression Analysis*

Risk Factor	Coefficient	SE	p	Significance of Regression (p)
Type of family†	0.685	0.176	<0.001	<0.001
Sex‡	0.950	0.171	<0.001	. . .
Drug treatment§	0.445	0.184	0.016	. . .
RRS	0.040	0.098	0.682	. . .

* As shown, the age at which myocardial infarction develops in relatives depends significantly on the set of risk factors analyzed. However only 3 of the 4 risk factors contribute significantly. The estimated regression coefficients with the standard error of the estimate are also shown. † Type of family (0 = control family; 1 = case family). ‡ Sex of relative (0 = female; 1 = male). § Drug treatment: presence (= 1) or absence (= 0) of drug treatment in patient or control subject. RRS = restricted cumulative risk score of patient or control subject (0 = lowest tertile; 1 = middle tertile; and 2 = highest tertile); SE = standard error.

improve the predictive value of that score. Neither did inclusion of smoking or smoking and age into the risk score. Other analyses were done on those without restricted risk score but with actual serum cholesterol, blood sugar, and systolic blood pressure as independent variables, as well as analyses of subsets of the data such as on relatives of patients and control subjects with and without drug or drug or diet treatment. The same picture always emerged: The *age* at which relatives had their first myocardial infarction did not so much depend on the known (genetic) risk factors in the proband as on other unknown factors distinguishing patient from control families.

Discussion

The question of how much of the familial aggregation of coronary heart disease is explained by the familial aggregation of hitherto-discovered risk factors has intrigued researchers for some time. In our present study we could confirm the higher risk level of patients compared with control subjects, but we were unable to discover more than faint indications of a correlation between the risk level and a family history of coronary heart disease.

The data presented herein are subject to certain considerations. First, when dealing with a retrospective study the possibility of misclassification with respect to risk factors exists because of past intervention. For instance, in this study blood pressure levels were similar for patients and control subjects. However, this intervention bias was taken into account by distinguishing between patients and control subjects with and without treatment. Only a minor effect on the data was apparent. Second, differential reporting of coronary events by patients and control subjects has often been suggested to be a source of bias in case-control studies. We therefore insisted, as much as possible, on interviewing the family members themselves or on inspecting death certificates. Because we failed to achieve this in 15% of patient relatives and 13% of control relatives, differential reporting cannot be ruled out completely, but more than a small effect seems unlikely. Third, blood bank donors may not be an ideal control group because they may be more healthy or health-conscious than the general population. If this were so, it would have enlarged the difference in risk level of patients and control subjects and, presumably, would have resulted in too large a role for risk factors compared with family history. Because it appeared that in our study risk factors did not predict coronary heart disease in relatives, this possible bias can be ignored.

According to our present study the clustering of coronary heart disease in families cannot be explained by the familial aggregation of hyperlipidemia, hypertension, diabetes, or smoking. Epstein[21] in 1967 speculated that the known degree of familial resemblance of serum cholesterol and blood pressure were insufficient to account for the familial clustering of coronary heart disease. Since then several studies have been devoted to the possible correlations between risk factors and familial occurrence of coronary heart disease. These studies differ greatly in methodology and study design. Starting from data obtained in prospective population studies, at least 3 approaches have been described. In the first approach[22,23] the family history of persons with low risk levels was compared with the family history of those with high risk levels. The second approach compared the risk levels of persons with a family history of coronary heart disease and the risk levels of those without such a family history.[24–27] In the third approach the study population was followed up for some time, and the predictive strength of risk factor levels and family history in relation to the incidence of new cases of coronary heart disease was studied.[28–31]

Case-control studies on the correlations between familial coronary heart disease and risk factors can be divided into 2 types: those starting from a series of patients who underwent coronary angiography, and those starting from a series of patients with clinical end points such as myocardial infarction or angina pectoris. In the first type of studies the study group is composed of patients with significant coronary obstruction whereas the control subjects are those who also underwent coronary angiography because of symptoms but did not show significant coronary obstruction.[32–35]

Although the attraction of these studies lies in the precise anatomic definition of coronary heart disease, these results are not completely applicable to clinical end points such as myocardial infarction. Dimsdale et al.[36] followed up a cohort of 189 men for 1 year after performance of angiography and determination of cardiovascular risk factors to ascertain which risk factors or clinical and laboratory findings could aid in predicting which patients would have a substantial cardiac morbid event later. Stepwise discriminant analysis revealed that a positive family history in first-degree relatives ranked third among all risk factors, right after the severity of angina and a history of previous myocardial infarction.

Apart from our present study, 2 case-control studies[9,37] starting from patients with clinical end-point manifestation of coronary heart disease have been described. These 2 studies reach completely different conclusions. Rissanen and Nikkilä[37] concluded that most of the familial aggregation of coronary heart disease is mediated by familial aggregation of hyperlipidemia or hypertension. This finding differs sharply from the conclusions of Nora et al.,[9] who incorporated family history along with other factors in their risk index. The Michigan Heart Association earlier also included family history as well as other risk factors in a risk index.[38]

With the exception of the report of Rissanen and Nikkilä,[37] earlier studies tend to be in accord with the findings presented here. It is possible that Rissanen and Nikkilä's findings are somehow specific for the Finnish population with its higher frequency of coronary risk factors.[39,40]

If other familial risk factors are postulated, how do they fit in the coronary risk profile as compared with

already known familial risk factors? The presently known risk factors are not mutually exclusive but exert their effect in an additive way.[41] The same may apply to the postulated unknown factors, but the present study does not solve this problem, nor does it establish to what extent the unknown familial risk factors have a genetic basis. Familial aggregation can be caused by genetic factors or by environmental factors common to family members, or by interaction of genetic susceptibility with specific environmental factors. For instance, the major risk factors may have a stronger impact on those with a familial predisposition. Future work will need to identify the specific familial factors that lead to familial aggregation of coronary heart disease. Unfortunately, at the time the study was designed, the role of high-density lipoprotein cholesterol was not recognized. Lipoprotein characteristics should be taken into account in future studies of familial clustering of coronary heart disease.[31] Other possible risk factors may be found in Hopkins and William's survey[42] of 246 suggested coronary risk factors.

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Assessment of Vasodilator Therapy in Patients With Severe Congestive Heart Failure: Limitations of Measurements of Left Ventricular Ejection Fraction and Volumes

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Although noninvasive techniques are often used to assess the effect of vasodilator therapy in patients with congestive heart failure, it is unknown whether changes in noninvasively determined left ventricular ejection fraction, volume, or dimension reliably reflect alterations in intracardiac pressure and flow. Accordingly, we compared the acute effect of sodium nitroprusside on left ventricular volume and ejection fraction (determined scintigraphically) with its effect on intracardiac pressure and forward cardiac index (determined by thermodilution) in 12 patients with severe, chronic congestive heart failure and a markedly dilated left ventricle. Nitroprusside (infused at 1.3 ± 1.1 [mean ± standard deviation] μg/kg/min) caused a decrease in mean systemic arterial, mean pulmonary arterial, and mean pulmonary capillary wedge pressure as well as a concomitant increase in forward cardiac index. Simultaneously, left ventricular end-diastolic and end-systolic volume indexes decreased, but the scintigraphically determined cardiac index did not change significantly. Left ventricular ejection fraction averaged 0.19 ± 0.05 before nitroprusside administration and increased by less than 0.05 units in response to nitroprusside in 11 of 12 patients. The only significant correlation between scintigraphically and invasively determined variables was that between the percent change in end-diastolic volume index and the percent change in pulmonary capillary wedge pressure (r = 0.68, p = 0.01). Although nitroprusside produced changes in scintigraphically determined left ventricular ejection fraction, end-systolic volume index, and cardiac index, these alterations bore no predictable relation to changes in intracardiac pressure, forward cardiac index, or vascular resistance. Furthermore, nitroprusside produced a considerably greater percent change in the invasively measured variables than in the scintigraphically determined ones.

Vasodilator therapy is widely used in severe congestive heart failure,[1-6] and the effects of sodium nitroprusside and other vasodilators are well characterized with invasive techniques.[7-11] More recently, several investigators have used echocardiography[12-15] or radionuclide ventriculography[15-21] to assess the efficacy of several vasodilators in these patients. Although these investigators assume that such a noninvasive assessment is reliable and sensitive, others[22,23] suggest that these noninvasive techniques may not reflect the hemodynamic changes that occur in response to therapy. Therefore, in the present study of patients with severe congestive heart failure, we simultaneously assessed the acute effect of sodium nitroprusside on intracardiac pressure, forward cardiac output (by thermodilution), and systemic and pulmonary vascular resistance as well as on radionuclide-determined left ventricular volume, ejection fraction, and cardiac index.

In so doing, we attempted to answer the following questions: In patients with severe congestive heart failure and a dilated left ventricle given nitroprusside: (1) Do alterations in scintigraphically determined left ventricular volume, ejection fraction, and cardiac index correlate with simultaneously measured changes in in-

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TABLE I Invasive Hemodynamic Measurements

	Heart Rate (beats/min)		THD Cardiac Index (liters/min/m^2)		Mean PCWP (mm Hg)		Mean PAP (mm Hg)		Mean FAP (mm Hg)		TPVR (dynes·s·cm^{-5})		TSVR (dynes·s·cm^{-5})	
Case	B	P	B	P	B	P	B	P	B	P	B	P	B	P
1	81	84	2.12	2.79	23	13	30	23	80	66	554	420	1,927	1,206
2	90	94	2.48	3.04	20	7	27	15	100	92	436	197	1,613	1,211
3	108	104	2.41	3.54	32	18	50	32	97	81	950	413	1,843	1,045
4	128	120	1.66	2.67	36	10	52	31	90	68	1,264	470	2,188	1,030
5	102	88	1.26	2.56	30	20	46	34	99	77	1,744	634	3,752	1,436
6	83	84	1.71	1.75	25	15	35	20	90	79	702	390	1,805	1,541
7	83	84	2.61	3.10	25	17	31	23	78	82	516	323	1,297	1,151
8	64	64	1.75	3.35	32	19	53	31	90	75	1,296	396	2,201	959
9	100	100	2.16	4.22	28	12	37	21	95	78	789	229	2,027	849
10	68	68	1.92	2.66	25	19	35	29	76	75	776	464	1,684	1,200
11	132	121	2.16	2.75	22	8	42	26	88	55	928	450	1,945	952
12	105	92	2.51	2.44	17	7	22	13	83	72	375	228	1,416	1,263
Mean	95	92	2.06	2.91	26	14	38	25	89	75	861	385	1,975	1,154
± SD	21	18	0.41	0.62	6	5	10	7	8	9	406	124	625	202
Mean Δ	−3		+0.84		−13		−14		−14		−476		−821	
Mean %Δ	−3.6		43.3		−47.5		−34.8		−15.6		−55.3		−41.6	
p	NS		<0.005		< 0.001		<0.001		<0.005		<0.001		<0.001	

B = baseline; FAP = femoral arterial pressure; P = peak nitroprusside infusion; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; THD = thermodilution; TPVR = total pulmonary vascular resistance; TSVR = total systemic vascular resistance.

TABLE II Multigated Blood Pool Imaging Data

	LV EF		LV EDVI (ml/m^2)		LV ESVI (ml/m^2)		Scan CI (liter/min/m^2)	
Case	B	P	B	P	B	P	B	P
1	0.12	0.16	216	213	190	180	2.03	2.69
2	0.26	0.27	110	76	82	57	2.52	1.88
3	0.20	0.19	115	108	93	89	2.38	1.98
4	0.22	0.25	159	81	125	61	4.35	2.40
5	0.13	0.15	185	175	162	150	2.35	2.29
6	0.19	0.19	145	124	117	103	2.24	1.76
7	0.27	0.30	233	204	170	145	5.23	4.96
8	0.25	0.27	280	213	211	156	4.42	3.65
9	0.15	0.30	220	148	187	105	3.30	4.30
10	0.14	0.18	280	231	241	191	2.65	2.72
11	0.20	0.22	113	105	91	83	2.90	2.78
12	0.20	0.24	162	150	133	115	3.15	3.22
Mean	0.19	0.23	185	152	150	120	3.13	2.89
± SD	0.05	0.05	61	55	51	45	1.02	0.99
Mean Δ	+0.03		−33		−31		−0.24	
Mean %Δ	+16.8		−17.6		−17.6		−8.0	
p	<0.005		<0.001		<0.001		NS	

B = baseline; CI = cardiac index; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; LV = left ventricular; P = peak nitroprusside infusion.

tracardiac pressure, forward cardiac index, or vascular resistances? (2) Which scintigraphically determined variable is the most reliable predictor of alterations in intracardiac pressure or forward cardiac index? (3) What is the relative magnitude of changes produced by nitroprusside in scintigraphically and invasively determined variables?

Methods

Patients

After informed consent was obtained, 12 patients (11 men and 1 woman, mean age 49 years) with New York Heart Association class III or IV congestive heart failure had cardiac catheterization according to the protocol detailed herein. All patients were in sinus rhythm, on maintenance digitalis and diuretics, and in some cases on antiarrhythmic agents; no patient was receiving other vasodilator agents. Most patients were thought to have idiopathic congestive cardiomyopathy, although some had a history of ethanol excess. Selective coronary angiography was performed in 10 patients; 2 had evidence of significant coronary artery disease (greater than 70% luminal diameter narrowing) involving 1 vessel in 1 patient and 2 vessels in the other. Radiographic (angiographic) evidence of mitral regurgitation was present in 11 patients, ranging from 1+ to 4+.[24] No patient had evidence of valvular stenosis or an intracardiac shunt.

Study Protocol

Cardiac catheterization: Cardiac catheterization was performed through the percutaneous Seldinger approach or brachial cutdown or both. Right heart catheterization was performed with a flow-directed, balloon-tipped thermodilution catheter (Electronics for Medicine thermodilution

TABLE III Relation Between Absolute Changes in Invasive and Multigated Blood Pool Data

	ΔTHDCI	ΔPCW	ΔPA	ΔFA	ΔTPVR	ΔTSVR
ΔLVEF	r = 0.53 NS	r = −0.14 NS	r = 0.07 NS	r = −0.01 NS	r = 0.01 NS	r = −0.14 NS
ΔLVEDVI	r = −0.55 NS	r = 0.53 NS	r = 0.46 NS	r = −0.08 NS	r = 0.35 NS	r = 0.14 NS
ΔLVESVI	r = −0.39 NS	r = 0.43 NS	r = 0.34 NS	r = −0.15 NS	r = 0.34 NS	r = 0.12 NS
ΔSCAN CI	r = 0.16 NS	r = 0.57 p = 0.05	r = 0.54 NS	r = 0.10 NS	r = 0.32 NS	r = 0.01 NS

Δ = absolute change; $\overline{FA}$ = mean femoral arterial pressure; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; NS = not significant; $\overline{PA}$ = mean pulmonary arterial pressure; $\overline{PCW}$ = mean pulmonary capillary wedge pressure; r = correlation coefficient; SCAN CI = cardiac index by multigated blood pool scan; THDCI = thermodilution cardiac index; TPVR = total pulmonary vascular resistance; TSVR = total systemic vascular resistance.

catheter 62 00 37) advanced to the pulmonary artery under fluoroscopic control. At baseline, multigated blood pool imaging was performed for 6 minutes, during which intracardiac pressures were recorded in duplicate, and forward cardiac output was measured by the thermodilution technique.[25] The average of 3 to 5 thermodilution measurements of forward cardiac output was used for the final computations. The variability of thermodilution measurements in our laboratory is ±4%.

After baseline measurements, intravenous sodium nitroprusside was infused at 0.25 μg/kg/min. A steady infusion was continued for 10 minutes, at which time pressure measurements, multigated blood pool imaging, and thermodilution cardiac output measurements were repeated. Subsequently, scintigraphic and hemodynamic measurements were accomplished after a 10 minute nitroprusside infusion at 0.50, 1.0, 2.0, and 4.0 μg/kg/min. The stepwise nitroprusside infusion was continued until pulmonary capillary wedge pressure decreased 35% or to an absolute level of 15 mm Hg. The maximal tolerated dose ranged from 0.25 to 4.0 μg/kg/min (mean 1.33). After nitroprusside infusion, left ventricular contrast angiography was performed in all patients.

Radionuclide ventriculography: Red blood cells were labeled with 30 mCi of technetium-99m sodium pertechnetate using a technique combining features of both in vitro and in vivo labeling.[26] Scintigraphic data collection was performed with a portable gamma scintillation camera (Series Sigma 420, Ohio Nuclear, Solon, Ohio), as previously described.[26–30] Left ventricular volume and ejection fraction were estimated by a totally nongeometric technique developed and validated in our laboratory.[26–28]

All volumes were normalized for body surface area. The interobserver and intraobserver variability of these volume measurements in our laboratory is 7.5 and 6%, respectively, and the reproducibility of these measurements over time has been substantiated.[29]

Statistical analysis: The mean ± standard deviation was determined for each variable at baseline and at peak nitroprusside infusion (Tables I and II). A paired *t* test was performed to compare changes in each variable between baseline and peak nitroprusside infusion. Nonparametric methods were used whenever unequal variances among groups were present.[31] A p value less than 0.05 was considered significant. Linear regression analysis was performed to compare the absolute change in each invasively determined variable with the absolute change in each variable determined by multigated blood pool scan (Table III) in response to nitroprusside. Similarly, linear regression analysis was performed to compare the percent change in each invasively measured variable with the percent change in each variable measured by multigated blood pool scan (Table IV) in response to nitroprusside. When more than 2 variables appeared interrelated, multivariate regression analysis was performed.

Results

Invasive hemodynamic measurements: The heart rate and invasively determined hemodynamic variables for each patient are shown in Table I. The heart rate averaged 95 ± 21 beats/min at rest and 92 ± 18 beats/min during peak nitroprusside infusion (difference not significant [NS]). The forward cardiac index (by thermodilution) increased from 2.06 ± 0.41 liter/min/m^2 at rest to 2.91 ± 0.62 during peak nitroprusside infusion ($p < 0.005$). Mean pulmonary capillary wedge pressure decreased from 26 ± 6 mm Hg before to 14 ± 5 at maximal nitroprusside infusion ($p < 0.001$), while mean pulmonary arterial pressure decreased from 38 ± 10 mm Hg to 25 ± 7 ($p < 0.001$). Similarly, mean femoral arterial pressure decreased from 89 ± 8 mm Hg to 75 ± 9 ($p < 0.005$). Total pulmonary vascular resistance averaged

TABLE IV Relation Between Percent Changes in Invasive and Multigated Blood Pool Data

	% Δ THD CI	% Δ PCW	% Δ PA	% Δ FA	% Δ TPVR	% Δ TSVR
% Δ LVEF	r = 0.41 NS	r = −0.16 NS	r = −0.01 NS	r = −0.07 NS	r = −0.19 NS	r = −0.30 NS
% Δ LVEDVI	r = −0.29 NS	r = 0.68 p = 0.01	r = 0.43 NS	r = 0.16 NS	r = 0.44 NS	r = 0.26 NS
% Δ LVESVI	r = −0.15 NS	r = 0.60 p = <0.05	r = 0.35 NS	r = 0.01 NS	r = 0.38 NS	r = 0.13 NS
% Δ SCAN CI	r = 0.13 NS	r = 0.32 NS	r = 0.42 NS	r = −0.01 NS	r = 0.32 NS	r = −0.08 NS

Abbreviations as in Table III.

861 ± 406 dynes·s·cm^{-5} and decreased to 385 ± 124 during maximal nitroprusside infusion ($p < 0.001$). Likewise, total systemic vascular resistance decreased in response to nitroprusside from 1,975 ± 625 dynes·s·cm^{-5} to 1,154 ± 202 ($p < 0.001$).

Multigated blood pool imaging measurements: The scintigraphically determined left ventricular ejection fraction, volumes, and cardiac index for individual patients are shown in Table II. Left ventricular ejection fraction averaged 0.19 ± 0.05 at baseline and increased slightly, but significantly, to 0.23 ± 0.05 during peak nitroprusside infusion ($p < 0.005$). However, the absolute increase in ejection fraction was greater than 0.05 units (the accepted limit of observer error)[32] in only 1 patient. The left ventricular end-diastolic volume index decreased in response to nitroprusside from 185 ± 61 to 152 ± 55 ml/m^2 ($p < 0.001$), whereas the end-systolic volume index decreased from 150 ± 51 ml/m^2 at baseline to 120 ± 45 during maximal nitroprusside infusion ($p < 0.001$). Cardiac index by multigated blood pool scan did not change significantly in response to nitroprusside (3.13 ± 1.02 liters/min/m^2 at baseline, 2.89 ± 0.99 during peak nitroprusside; NS).

Invasive versus multigated blood pool data: The relation between the absolute change in each invasively determined variable and each measurement determined by multigated blood pool imaging for individual patients is shown in Table III. Only 1 group of variables approached a significant correlation, namely, the absolute change in mean pulmonary capillary wedge pressure and the absolute change in cardiac index determined by multigated blood pool scan ($r = 0.57$, $p = 0.05$). However, because 24 such comparisons were performed, this chance finding might be anticipated. The spurious nature of this apparent correlation is further emphasized by the fact that although pulmonary capillary wedge pressure decreased markedly, cardiac index by gated blood pool scan did not change significantly. Thus, no correlation appears to exist between the absolute change in any of the invasively determined measurements and those determined by multigated blood pool scan.

The relation between the percent change in invasive measurements and that in radionuclide measurements is shown in Table IV. There was a significant correlation between the percent change in pulmonary capillary wedge pressure and that in left ventricular end-diastolic volume index ($r = 0.68$, $p = 0.01$) as well as the percent change in left ventricular end-systolic volume index ($r = 0.60$, $p < 0.05$). However, the percent change in end-diastolic volume and that in end-systolic volume are themselves highly correlated ($r = 0.89$, $p < 0.001$). Trivariate regression analysis, comparing the percent change in pulmonary capillary wedge pressure (PCW) and end-diastolic (EDVI) and end-systolic (ESVI) volume indexes (PCW = 31.9 − 0.067 [ESVI] + 0.8088 [EDVI]), suggests that the primary correlation is between the percent change in pulmonary capillary wedge pressure and the percent change in end-diastolic volume index. However, the statistical significance of even this correlation is in question when the Bonferroni adjustment for multiple comparisons is applied.[31] The relation between the percent change in pulmonary capillary wedge pressure and end-diastolic volume index as well as the 95% confidence limits is shown in Figure 1. There was no significant relation between the percent change in any other invasively measured and scintigraphically determined variable.

Discussion

In patients with congestive heart failure, vasodilator therapy is considered effective when it causes an increase in forward cardiac output or a decrease in pulmonary vascular congestion, or both, without associated systemic arterial hypotension. Although changes in noninvasively determined left ventricular volume, cardiac output, and ejection fraction are often used to evaluate the response to vasodilator therapy,[12–21] the exact relation between changes in these variables and alterations in invasively determined ones in patients with severe congestive heart failure has not been characterized. In particular, it is not clear whether changes in pulmonary capillary wedge pressure, pulmonary arterial pressure, or forward cardiac output are related to changes in any of the variables measured by radionuclide ventriculography. Therefore, the present study was performed to assess the relation between changes in variables measured by radionuclide ventriculography and those determined invasively in patients with severe congestive heart failure given sodium nitroprusside.

Changes in radionuclide and invasive measurements: In the present study, nitroprusside produced a hemodynamic response similar to that reported previously[7–11]: forward cardiac index increased, whereas mean pulmonary capillary wedge, mean pulmonary arterial, and mean femoral arterial pressures decreased. Total pulmonary vascular and systemic vascular resistances decreased, whereas heart rate did not change significantly (Table I). Simultaneously, mean left ventricular ejection fraction increased from 0.19 to 0.23, an observation that would seem to lend credence to the use of this variable in assessing the efficacy of vasodilator therapy.[16–19] Although this change is statistically significant, its clinical relevance is questionable because the absolute change is less than 0.05 units (the accepted variability of absolute ejection fraction for repetitive studies in abnormal patients)[32] in 11 of the 12 patients. Finally, nitroprusside caused a progressive decrease in both end-diastolic and end-systolic volume indexes but no change in total cardiac index as measured by radionuclide ventriculography.

Changes in invasive versus noninvasive measurements: The absolute changes in forward cardiac index, mean pulmonary capillary wedge, pulmonary arterial, and femoral arterial pressures, and total pulmonary and systemic vascular resistances produced by nitroprusside bore no relation to the absolute changes in left ventricular ejection fraction, end-diastolic volume index, end-systolic volume index, and cardiac index by radionuclide ventriculography (Table III). When changes in the invasively and noninvasively determined variables were expressed as percentages, the only sig-

nificant correlation was between the percent change in left ventricular end-diastolic volume index and the percent change in mean pulmonary capillary wedge pressure (Table IV). Although the correlation coefficient for this relationship is 0.68, the 95% confidence limits are wide (Fig. 1). In addition, the large negative intercept implies that a reduction in pulmonary capillary wedge pressure of more than 30% might occur without a change in end-diastolic volume index. None of the radionuclide measurements was predictive of the observed increase in forward cardiac output.

The observed disparity between the changes in radionuclide and invasive measurements suggests 1 of 2 possibilities. First, the radionuclide technique may be intrinsically invalid in patients with severe congestive heart failure. We cannot exclude this possibility because we have not compared ventricular volumes measured by radionuclide and contrast ventriculography in patients with a low ejection fraction. However, previous investigators[33] showed an excellent correlation between radionuclide and contrast angiographic measurements of left ventricular ejection fraction, even in those with severe left ventricular dysfunction and ejection fraction less than 0.30. Furthermore, we[30] previously demonstrated that radionuclide and contrast angiographic measurements of left ventricular volumes correlate closely, even in patients with a markedly dilated left ventricle (due to aortic regurgitation). In light of the aforementioned data, it seems reasonable to assume that both left ventricular ejection fraction and absolute volumes can by measured accurately using a count-based, nongeometric radionuclide ventriculographic technique in these patients.

In patients with severe congestive heart failure, the validation of the radionuclide-determined stroke volume by another technique (such as thermodilution stroke volume measurements) is problematic. Because mitral regurgitation is an almost invariable accompaniment of severe congestive heart failure, total cardiac output (as measured by radionuclide ventriculography) exceeds forward cardiac output. Thus, in these patients the radionuclide measurement of cardiac output cannot be validated by comparing it with a measurement of forward cardiac output. In the present study, 11 of the 12 patients had angiographic evidence of mitral regurgitation (1 to 4+). As a result, the lack of correlation between radionuclide-determined (total) and thermodilution-determined (net forward) cardiac index in this study is not unexpected.

Second, it is conceivable that both the radionuclide and the invasive techniques are measuring changes accurately but that the changes measured are not linearly related to one another. A major reason for the poor correlation between changes in left ventricular volume and changes in filling pressure may be that nitroprusside alters left ventricular compliance.[9] In the present study, left ventricular end-diastolic and end-systolic volume indexes decreased in each patient, but left ventricular ejection fraction behaved less predictably. This finding is particularly noteworthy because changes in left ventricular ejection fraction by radionuclide ventriculography have been widely used[15–21] to assess the effects of vasodilator therapy. The disparity between the changes in left ventricular ejection fraction and the changes in invasive measurements can be explained in several ways: (1) Changes in ejection fraction may be measured accurately but fall within the limits of resolution of the system used for their detection. In 11 of 12 patients the detected change was less than the accepted limit of observer error (0.05 units). (2) Even if the radionuclide technique is valid, the detection of small changes in a large ventricle is likely to be less accurate than the detection of the same magnitude of change in a small ventricle. (3) The differential effects of nitroprusside on preload and afterload in patients with various degrees of mitral regurgitation might produce various effects on left ventricular ejection fraction. Conceptually, reduction of the effective mitral orifice size[34,35] and removal of a low impedance outlet (by predominant preload reduction) might result in a decrease in left ventricular ejection fraction; alternatively, a predominant afterload reduction might result in an increase in ejection fraction. Although our suggestion that left ventricular ejection fraction might decrease because of a predominant preload effect is purely hypothetical, a reduction in the left ventricular ejection fraction after mitral valve replacement for mitral regurgitation is well documented.[36] Each of these 3 factors may play some role in rendering the left ventricular ejection fraction of limited value in assessing the effect of vasodilators in the individual patient with severe congestive heart failure.

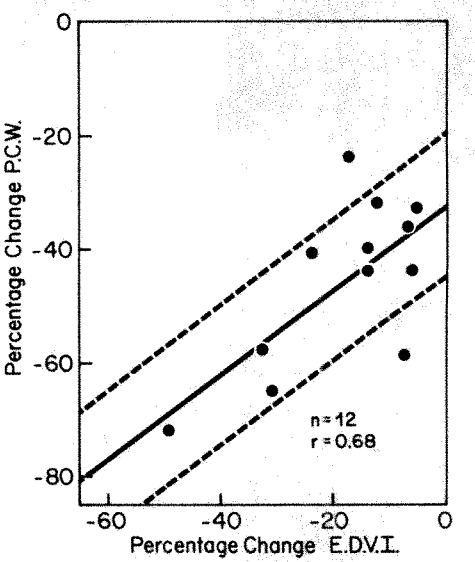

FIGURE 1. The percent change in pulmonary capillary wedge pressure (PCW) versus the percent change in left ventricular end-diastolic volume index (EDVI) in response to nitroprusside infusion. The 95% confidence limits of the intercept are shown. Although the correlation between these 2 variables is acceptable, the large negative intercept implies that a reduction in pulmonary capillary wedge pressure of more than 30% might occur without a change in end-diastolic volume index.

Two points about the present study deserve emphasis. First, it attempts to explore the effects of *acute* vasodilator therapy (with sodium nitroprusside) on both

hemodynamic and scintigraphic variables in a well-controlled setting free from motion artifact (such as might occur during exercise). Second, the patients comprising this study had severe left ventricular dysfunction; in addition, most had mitral regurgitation due to left ventricular dilatation. It is conceivable that patients with less severe left ventricular dysfunction as well as those without associated mitral regurgitation might respond differently to nitroprusside. However, mitral regurgitation due to ventricular dysfunction is an almost invariable finding in precisely the patients in whom nitroprusside and other vasodilators are most likely to be used.

Clinical implications: In patients with severe congestive heart failure and a greatly enlarged left ventricle, marked hemodynamic changes may occur without detectable changes in left ventricular ejection fraction. Although acute nitroprusside infusion causes a reduction in both left ventricular end-diastolic and end-systolic volume (measured by radionuclide ventriculography), these changes cannot readily be used to predict alterations in pulmonary capillary wedge pressure or forward cardiac output.

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Effects of Acute and Chronic Minoxidil Administration on Rest and Exercise Hemodynamics and Clinical Status In Patients With Severe, Chronic Heart Failure

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The effects of acute and chronic oral administration of the vasodilator minoxidil on hemodynamics, oxygen consumption, exercise performance, and clinical status were investigated in 10 patients with severe, chronic heart failure refractory to digitalis and diuretic therapy. The cardiac index was 1.99 ± 0.38 liters/min/m^2 at rest and 2.88 ± 0.79 at symptom-limited maximal exercise on conventional therapy, compared with 2.64 ± 0.33 liters/min/m^2 at rest and 3.55 ± 0.84 at maximal exercise after short-term minoxidil administration ($p < 0.02$, control versus minoxidil at both rest and exercise). Stroke volume was increased after minoxidil treatment, without significant effect on heart rate. Systemic vascular resistance was decreased by minoxidil from 2,050 ± 722 to 1,325 ± 374 dynes·s/cm^{-5} at rest and from 1,500 ± 830 to 1,206 ± 589 dynes·s/cm^{-5} at maximal exercise ($p = 0.01$, control versus minoxidil). No significant effect was observed on left ventricular filling, right atrial, or mean pulmonary arterial pressure, but pulmonary vascular resistance decreased both at rest and on exercise ($p < 0.05$). Maximal exercise oxygen consumption increased from 8.9 ± 3.2 ml/kg/min on conventional therapy to 10.5 ± 2.4 on minoxidil therapy ($p < 0.03$), median maximal exercise work load increased from 25 to 50 W and median exercise duration increased from 6.0 to 9.0 minutes. On chronic minoxidil administration all 5 patients who completed a scheduled 6 week follow-up showed symptomatic improvement. However, worsening edema developed in all patients, requiring increased diuretic dosage and close supervision. Symptoms of ischemic heart disease worsened in 2 of 10 patients. We tentatively conclude that minoxidil may be a useful vasoactive agent in the pharmacologic therapy of severe chronic heart failure.

Administration of vasoactive drugs to patients with severe chronic congestive heart failure refractory to conventional therapy with digitalis and diuretics has been shown to result in salutary hemodynamic and clinical effects.[1,2] However, there is no consistent evidence that short-term administration of vasodilator drugs, including nitrates,[3] prazosin,[4,5] hydralazine,[6,7] and combination therapy[8,9] improve maximal oxygen consumption or exercise performance. There is also a scarcity of data from controlled clinical trials suggesting any long-term benefit from vasodilators in heart failure.

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Previous preliminary reports have demonstrated beneficial effects of the direct-acting arteriolar vasodilator minoxidil in patients with chronic congestive heart failure at rest.[10–12] The effects of short-term minoxidil administration on exercise hemodynamics or performance and the effects of chronic minoxidil administration on clinical outcome have not previously been reported in patients with severe chronic heart failure. The purpose of this study was to investigate the hemodynamic and clinical effects of short-term minoxidil therapy on the exercise performance of patients with severe chronic heart failure.

Methods

Study population: The study population consisted of 10 patients, 7 men and 3 women, with a mean age of 65 years (range 44 to 77). The cause of chronic heart failure was ischemic heart disease in 8 patients and idiopathic cardiomyopathy in 2. Six patients had previous aortocoronary bypass grafting, and of this group 2 had mitral valve replacement

and 1 had aortic valve replacement. Prosthetic valve function was normal in these 3 patients. Symptoms of heart failure were present for a median duration of 28 months (range 1 to 84) before entry into the study. All patients gave a history of slowly worsening symptoms before entry into the study despite empirical optimization of therapy with digitalis and diuretics. No patient had acute pulmonary edema or myocardial infarction within the month before admission. At the time of admission, all patients were in New York Heart Association (NYHA) functional class III or IV.[13] The mean digoxin dose was 0.18 mg/day and the mean furosemide dose was 118 mg/day (range 40 to 160). No patient had current symptoms of angina pectoris. Four patients had previously received a trial of vasodilator therapy (1 patient prazosin and 3 patients hydralazine) but all vasoactive medication was withdrawn at least 48 hours before entry into the study. No patient had clinically severe mitral regurgitation, but 3 patients had clinical evidence of tricuspid regurgitation from secondary right heart failure. The resting left ventricular ejection fraction measured by the gated equilibrium blood pool technique[14] was severely depressed in all patients, with a mean value of 0.20 ± 0.07.

All patients were hospitalized in the coronary care unit a minimum of 48 hours before study initiation. During this time dietary sodium intake was restricted, and stable doses of digitalis and diuretics were administered. This protocol was approved by the Human Subjects committee of this institution. Signed, informed consent was obtained from all patients.

Hemodynamic measurements and oxygen consumption: A Swan-Ganz balloon flotation thermodilution catheter was inserted percutaneously from the internal jugular vein in all patients. Cardiac output (liters/minute) was measured in duplicate by thermodilution in 8 patients and by the Fick principle in 2 patients. The correlation between these 2 techniques in our laboratory is 0.91 at rest and 0.92 at exercise, and is not affected by the presence or absence of tricuspid regurgitation (unpublished observations). Left ventricular filling pressure (LVFP, mm Hg) was estimated by the mean pulmonary capillary wedge pressure or pulmonary arterial diastolic pressure, the method remaining constant for a given patient. Blood pressure (mm Hg) was measured using an indwelling radial artery cannula. Heart rate (beats/minute) was recorded from the electrocardiogram at the time of cardiac output determination. Systemic vascular resistance (SVR, dynes·s/cm^{-5}) was calculated as SVR = $[(\overline{MAP} - \overline{RA})/CO] \times 80$, where MAP = mean arterial pressure, $\overline{RA}$ = mean right atrial pressure, and CO = cardiac output. Pulmonary vascular resistance (PVR) was calculated as PVR = $[(\overline{PA} - LVFP)/CO] \times 80$, where $\overline{PA}$ = mean pulmonary arterial pressure.

Oxygen saturation (fraction) and hemoglobin concentration (g/dl) were measured spectrophotometrically (Instrumentation Laboratories #282 Co-oximeter). Oxygen content (ml O_2/dl) was calculated as oxygen saturation fraction × hemoglobin concentration ×1.34. Arteriovenous oxygen content difference (A-VO_2, ml O_2/dl) was calculated as $C_a - C_v$, where C_a = arterial oxygen content and C_v = mixed venous (pulmonary arterial) oxygen content.

Oxygen consumption ($\dot{V}O_2$, ml O_2/kg/min, standard temperature and pressure, dry) was measured by analysis of expired gas. Timed collections of expired gas were made through a low resistance 2-way valve (modified Otis-McKerrow, Collins Corporation, Cambridge, Massachusetts) into latex meteorologic balloons. Three minute gas collections were made at rest and 1 to 2 minute collections made at peak exercise. Gas analysis was performed soon after collection using a mass spectrometer (Perkin-Elmer, MGA 1100, Pomona, California) for fractional gas concentration determination and a gasometer for volume determination.

Exercise protocol: Sequential measurements at rest and during exercise were made in the postabsorptive state at about the same time of day. A trial exercise period was performed the day before formal entry into the study to familiarize the patient with the procedure. The patient sat upright on the cycle ergometer (Monark), and his feet were secured to the pedals. After at least 10 minutes of equilibration, resting measurements were recorded. Progressive cycle exercise was performed to symptom-limited maximum using successive workload increments of 25 W at consecutive 3 minute intervals. Initial work load was zero load. All patients pedaled at a constant speed of 44 revolutions/min to ensure a constant workload. Expired gas collection and measurement of hemodynamic variables were performed during the last minute of peak exercise effort.

At peak exercise, all patients reported severe general body fatigue, severe leg discomfort, and moderate to severe dyspnea. No exercise test was stopped because of chest pain or dysrhythmia. For all patients, the respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$, the quotient of carbon dioxide production and oxygen consumption) was increased significantly at peak exercise (mean 1.07) compared with resting conditions, indicating that patients had achieved anaerobic threshold. Thus, oxygen consumption at peak exercise probably represented a close approximation to the true maximal $\dot{V}O_2$.[15]

Drug protocol: Doses of digoxin and furosemide were kept constant during the addition of minoxidil therapy. Because the pharmacologic half-life of minoxidil is 12 to 18 hours, an incremental dosage schedule was designed in order to minimize the probability of an undesirable hemodynamic effect. The initial test dose of 2.5 mg was given orally, and supine hemodynamic measurements were recorded serially every 30 minutes. Additional doses of minoxidil were administered every 90 minutes in log-dose fashion; the second dose was 2.5 mg, the third 5.0 mg, the fourth 10 mg, and so on. We used a hemodynamic end point of an increase in supine, resting cardiac output of at least 25% over baseline value. All patients achieved that end point during initial dose titration without demonstrating the previously defined withdrawal criteria of systolic blood pressure less than 90 mm Hg or heart rate greater than 120 beats/min. Subsequent doses were calculated

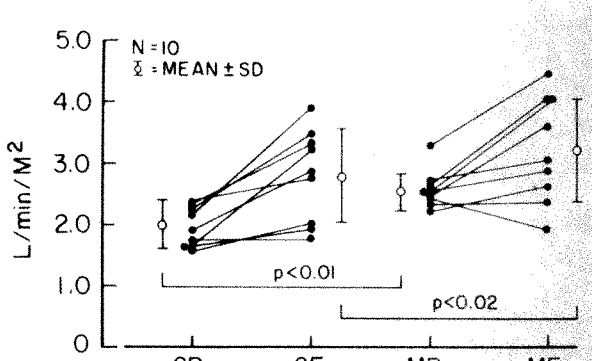

FIGURE 1. Effect of short-term minoxidil therapy on cardiac index at rest and exercise in patients with chronic heart failure. Cardiac index (liters/min/m^2) is represented on the **ordinate.** CE = conventional therapy at peak exercise; CR = conventional therapy at rest; ME = minoxidil therapy at peak exercise; MR = minoxidil therapy at rest; SD = standard deviation.

TABLE I Hemodynamic and Oxygen Consumption Measurements in 10 Patients With Severe Chronic Heart Failure

Case	Age (yr)	Cond	CI (liters/min/m²)	SVI (ml/beat/m²)	HR (beats/min)	LVFP (mm Hg)	$\dot{V}O_2$ (ml/kg/min)	SVR (dynes·s/cm⁻⁵)	PVR (dynes·s/cm⁻⁵)	$\overline{PA}$ (mm Hg)	$\overline{RA}$ (mm Hg)	A-VO_2 (ml/dl)	$\overline{AP}$ (mm Hg)
1	62	CR	2.16	30.4	71 (VP)	12	3.0	1,288	108	18	2	6.6	75
		CE	3.90	54.9	71 (VP)	18	10.0	704	110	29	2	12.8	72
		MR	2.45	27.5	89	18	3.0	1,218	64	22	2	5.2	78
		ME	4.08	42.9	95	19	9.9	692	96	29	5	10.4	77
2	68	CR	1.66	14.4	115	22	3.7	3,589	182	28	5	8.1	115
		CE	1.93	16.4	118	28	6.7	3,200	288	39	9	11.3	118
		MR	2.34	22.1	106	22	4.0	2,205	108	27	4	5.5	106
		ME	2.35	21.4	110	26	8.6	2,350	194	35	8	10.4	117
3	70	CR	2.26	28.6	79	12	3.9	2,142	196	20	20	6.6	111
		CE	3.52	32.9	107	32	14.1	1,542	189	47	47	14.8	131
		MR	3.30	37.5	88	12	3.7	1,147	147	21	21	5.0	88
		ME	4.51	40.3	112	28	14.3	973	117	40	40	12.9	113
4	68	CR	2.61	26.6	98	21	4.9	1,259	230	36	2	8.3	84
		CE	3.36	29.5	114	33	10.8	1,061	238	53	2	15.5	91
		MR	2.52	23.8	106	10	4.3	1,193	223	24	2	7.5	77
		ME	3.64	32.2	113	26	11.9	715	198	44	12	16.3	80
5	77	CR	1.90	18.4	103	31	4.6	2,227	151	38	2	9.9	105
		CE	2.88	25.0	115	34	9.2	1,426	120	48	13	13.0	113
		MR	2.26	23.1	98	16	3.9	1,687	145	24	2	6.5	95
		ME	2.65	24.5	108	34	10.0	1,541	169	37	2	12.9	111
6	67	CR	2.39	29.5	81 (VP)	16	3.9*	1,235	133	23	2	5.8	67
		CE	2.79	34.4	81 (VP)	22	6.4*	1,138	179	33	10	8.2	80
		MR	2.74	33.8	81 (VP)	18	4.0*	929	182	29	8	5.2	65
		ME	3.06	37.8	81 (VP)	24	7.1*	1,039	222	39	10	8.3	80
7	44	CN	1.61	19.2	84	36	3.8	2,143	486	53	15	9.8	90
		CE	3.24	35.6	91	46	12.0	908	227	62	31	17.0	95
		MR	2.68	26.3	102	32	4.4	1,236	240	46	15	6.4	87
		ME	4.08	36.0	113	46	13.3	786	186	64	32	14.6	108
8	66	CR	1.42*	16.9	84	18	3.1	2,428	311	28	8	7.8	89
		CE	1.83*	16.2	113	23	5.4	1,767	368	38	16	11.8	88
		MR	2.57*	27.6	93	17	3.4	1,281	350	35	20	5.5	86
		ME	2.92*	24.5	119	20	8.5	1,182	343	40	21	11.4	90
9	76	CR	1.77	21.1	84	26	2.3	2,449	462	43	17	8.4	107
		CE	1.75	13.9	126	43	3.8	2,538	552	63	25	14.1	117
		MR	2.45	30.4	84	16	2.5	1,376	295	33	7	6.4	77
		ME	1.93*	. . .	99	26	. . .	2,050	450	44	18	10.9	100
10	52	CR	2.16	25.7	84	10	3.3	1,739	251	15	2	5.9	92
		CE	3.56	37.5	95	14	10.6	1,160	152	20	2	10.9	101
		MR	3.08	31.8	97	8	4.5	974	149	13	2	4.8	74
		ME	4.69	45.1	104	13	11.1	729	98	18	2	9.1	84
Mean ± SD													
CR			1.99 ±0.38	23.1 ±5.8	88 ±13	20 ±9	3.7 ±0.8	2,050 ±722	251 ±132	30 ±12	8 ±7	7.7 ±1.5	94 ±16
CE			2.88 ±0.79	29.6 ±12.4	103 ±18	29 ±10	8.9 ±3.2	1,544 ±777	242 ±134	43 ±14	16 ±15	12.9 ±2.5	101 ±19
MR			2.64 ±0.33†	28.4 ±5.0†	94 ±9	17 ±7	3.8 ±0.6	1,325 ±374†	190 ±87†	27 ±9	8 ±8	5.8 ±0.9†	83 ±12†
ME			3.55 ±0.84‡	33.9 ±8.7	105 ±11	26 ±9	10.5 ±2.4‡	1,206 ±589	207 ±112‡	39 ±12	15 ±13	11.7 ±2.5‡	96 ±16

All data are expressed as mean ± standard deviation (SD).

* Fick cardiac output. † $p < 0.05$ minoxidil treatment compared with control at rest. ‡ $p < 0.05$ minoxidil treatment compared with control during exercise.

AP = mean arterial pressure; A-VO_2 = arteriovenous oxygen content difference; CE = conventional therapy at peak exercise; CI = cardiac index; Cond = condition of measurement; CR = conventional therapy at rest; HR = heart rate; LVFP = left ventricular filling pressure; ME = minoxidil therapy on exercise; MR = minoxidil therapy at rest; PA = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; RA = mean right atrial pressure; SVI = stroke volume index; SVR = systemic vascular resistance; $\dot{V}O_2$ = oxygen consumption.

as the sum of the titration doses and administered every 12 hours. The mean dose administered was 15.2 mg (range 7.5 to 22.5). Repeat exercise testing after short-term minoxidil therapy was performed 2 hours after the fifth dose. In 1 patient an unstable pattern of angina pectoris developed during minoxidil therapy before the second exercise test, and the patient could not be entered into the study. Minoxidil was administered to 2 additional patients under the same protocol, but the pulmonary arterial catheter was removed because of infection before repeat exercise testing on the drug; data from these patients are also not included in the present series. Both of these patients had increased resting cardiac output without side effects.

Data analysis: Comparisons between treatment groups and between rest and exercise conditions were made using a 2-factor analysis of variance (ANOVA) for repeated measures. Significant interaction effects were confirmed by the Newman-Keuls test for comparisons. The level of significance was chosen as 0.05.

Results

Individual patient data are summarized in Table I.

Cardiac output: During conventional therapy, the cardiac index increased from 1.99 ± 0.38 liters/min/m^2 at rest to 2.88 ± 0.79 at peak exercise. After minoxidil therapy, the cardiac index increased to 2.64 ± 0.33 liters/min/m^2 at rest and 3.55 ± 0.84 at maximal exercise. As shown in Figure 1, the increases in cardiac index were statistically significant both at rest and on exercise ($p < 0.02$). Thus, minoxidil primarily increased cardiac output at rest and did not blunt the additional increase due to exercise. Drug treatment and exercise contributed independently to the increase in cardiac output seen with exercise in patients in the drug-treated group. No significant statistical interaction effects were found.

The relative contributions of heart rate and stroke volume to cardiac output were examined next (Fig. 2). With conventional therapy, the heart rate increased from 88 ± 13 beats/min at rest to 103 ± 18 at peak exercise. After minoxidil treatment, the heart rate was not significantly different ($p < 0.10$) from conventional therapy either at rest (94 ± 9 beats/min) or on maximal exertion (105 ± 11). However, at rest 3 patients had an increase in heart rate of more than 10 beats/min after minoxidil. The stroke volume index was 23.1 ± 5.8 ml/beat/m^2 at rest and increased to 29.6 ± 12.4 at peak exercise during conventional therapy. After the addition of minoxidil, the stroke volume index increased significantly ($p < 0.02$) to 28.4 ± 5.0 ml/beat/m^2 at rest and 33.9 ± 8.7 at maximal exercise. In two patients, stroke volume decreased slightly at rest after minoxidil. The cardiac index was preserved by a slight increase in heart rate.

No interaction between drug treatment and exercise was found for stroke volume. These data suggest that the major effect of minoxidil is to increase stroke volume to a similar degree both at rest and on exercise, without a substantial effect on heart rate.

Systemic and intracardiac pressure and resistance: During conventional therapy, mean arterial pressure increased from 94 ± 16 at rest to 101 ± 19 mm Hg at peak exercise. After the addition of minoxidil, mean arterial pressure was lower but still increased from 83 ± 12 at rest to 96 ± 16 mm Hg at peak exercise. The small decrease in resting blood pressure when minoxidil was added was significant ($p < 0.05$) and was more than 15 mm Hg in 3 patients although no patient had symptomatic hypotension. At peak exercise, there was no significant change ($p > 0.10$) in mean arterial pressure after minoxidil administration. However, there was a significant drug-exercise statistical interaction ($p < 0.02$), indicating that the increase in mean arterial pressure from rest to exercise was actually higher after minoxidil treatment than on conventional therapy.

During conventional therapy, systemic vascular resistance fell during exercise from 2,050 ± 722 to 1,500 ± 830 dynes·s/cm^5 (p = NS). During minoxidil therapy, systemic vascular resistance decreased from 1,325 ± 374 to 1,206 ± 589 dynes·s/cm^5 (p = NS). There was a significant statistical interaction between minoxidil and exercise such that the reduction in systemic vascular resistance from rest to exercise was blunted by minoxidil ($p < 0.05$).

Left ventricular filling pressure was elevated at 20 ± 9 mm Hg on conventional therapy and increased further with exercise to 29 ± 10 mm Hg. After the addition of minoxidil, there was no significant change in left ventricular filling pressure at rest or exercise. However, changes in mean filling pressure were erratic, and 4 patients had a decrease of more than 10 mm Hg at rest after minoxidil.

Pulmonary vascular resistance was elevated in the patients while on conventional therapy at 251 ± 132 dynes·s/cm^5, and did not change with exercise (242 ± 134, p = NS). The addition of minoxidil significantly decreased pulmonary vascular resistance both at rest (190 ± 87 dynes·s/cm^5) and on exercise (207 ± 112) ($p < 0.05$).

Oxygen consumption and exercise performance: Oxygen consumption measured at rest was 3.7 ± 0.8 ml/kg/min, which indicated that the total body metabolic requirements for oxygen at rest were not signifi-

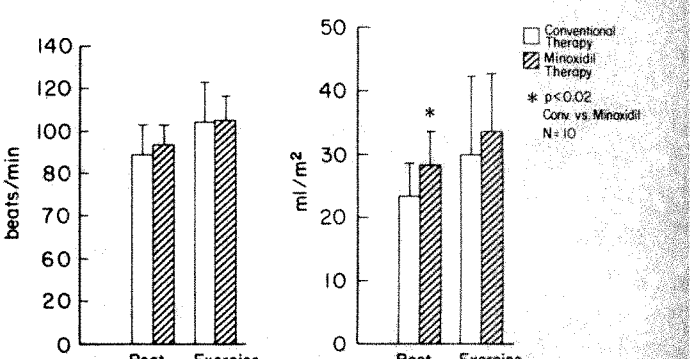

FIGURE 2. Effect of short-term oral minoxidil administration on heart rate (**left**) and stroke volume (**right**) at rest and exercise in patients with severe heart failure. **Open bars** represent values on conventional therapy alone; **cross-hatched bars** represent values after the addition of minoxidil. There was a significant increase in resting stroke volume ($p < 0.02$) after minoxidil treatment.

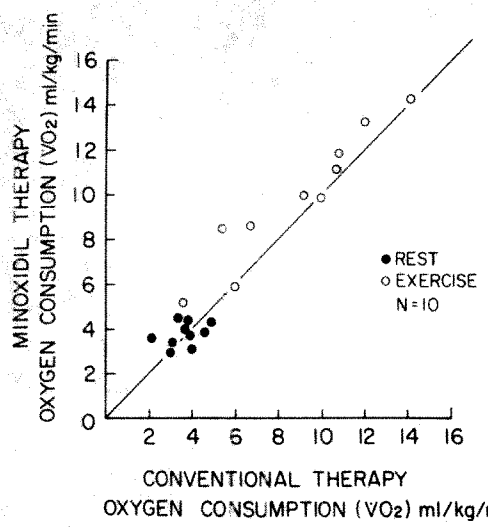

FIGURE 3. Effect of minoxidil therapy compared with conventional therapy on peak oxygen consumption in patients with severe chronic heart failure. Each **point** represents the peak oxygen consumption for the same patient while on conventional therapy and after the addition of minoxidil. **Solid circles** indicate resting conditions and **open circles** indicate maximal symptom-limited exercise. The **solid line** is the line of identity. Six of 10 patients showed higher peak $\dot{V}O_2$ on minoxidil therapy compared with conventional therapy (that is, data points above the line of identity).

cantly different from normal in these patients. Resting oxygen consumption was unchanged (3.8 ± 0.6 ml/kg/min) after the addition of minoxidil. Oxygen consumption at maximal exercise only increased to 8.9 ± 3.2 ml/kg/min on conventional therapy. After administration of minoxidil, maximum oxygen consumption was 18% higher (10.5 ± 2.4 ml/kg/min) than with conventional therapy. As shown in Figure 3, six of 10 patients had slightly improved maximal oxygen consumption after minoxidil therapy. These data principally reflect an increase of 1 work load stage in 4 of the patients. During conventional therapy, the median peak exercise work load was 25 W (range 0 to 75) and the median exercise duration was 6.0 minutes (range 3 to 12). After the addition of minoxidil, the median peak work load increased to 50 W (range 0 to 75) at a median exercise duration of 9.0 minutes (range 3 to 12).

Minoxidil decreased the arteriovenous oxygen content difference at rest from 7.7 ± 1.5 to 5.8 ± 0.9 ml O_2/dl blood ($p < 0.001$) and on exercise from 12.9 ± 2.5 to 11.7 ± 2.5 ($p < 0.001$). Therefore, minoxidil increased cardiac output at rest and on exercise and oxygen consumption on exercise despite a narrowing of the arteriovenous oxygen content difference. Arterial oxygen saturation was normal and nearly fully saturated at rest and on exercise (0.95 ± 0.01), and was unchanged by minoxidil.

Clinical follow-up during long-term minoxidil therapy: Clinical follow-up was planned for 6 weeks. However, only 5 of 10 patients completed the entire follow-up period. Minoxidil was discontinued because of an intercurrent subendocardial myocardial infarction in 1 patient, and 4 other patients refused to comply with the outpatient protocol, which required frequent return clinic visits and medication adjustment. All of the remaining patients reported symptomatic improvement of at least 1 functional class. No patient had symptomatic hypotension or tachycardia.

All patients developed worsening dependent edema which required continued dietary sodium restriction and increased diuretic dosage to maintain a stable body weight. At the sixth week of therapy, the mean furosemide dose was 220 mg/day, compared with a mean dose of 118 mg/day before minoxidil administration. One patient required concomitant daily administration of 5 mg of metolazone. The only female patient in the follow-up group developed increased facial hair growth, which was treated with a calcium thioglycollate depilatory.[16] Angina pectoris also developed while she was taking minoxidil, but improved when the drug was discontinued after the 6 week trial period. Another patient developed worsening of an antecedent benign essential tremor, which responded to low doses of oral diazepam. No other side effects of minoxidil were observed in our patient cohort.

Since minoxidil administration has been associated with the development of pericardial effusion in some patients with hypertension,[17] serial M-mode echocardiograms were obtained to detect this potential complication. Two patients had small effusions before minoxidil therapy, which did not change during drug administration. None of the remaining patients, including the 4 patients observed for the entire 6 weeks, had a new pericardial effusion.

Discussion

Minoxidil is a direct-acting arteriolar vasodilator that may have several advantages over other currently available compounds of this class. In hypertensive patients it is a powerful peripheral vasodilator which may be efficacious even when a patient does not respond to other drugs, including hydralazine. It has a prolonged duration of action and can be administered on a once- or twice-daily schedule, which can increase patient compliance. It has no direct chronotropic or inotropic activity. The drug does not appear to result in orthostatic hypotension. Also, it is chemically distinct, and unlike hydralazine is not associated with a lupus-like syndrome or peripheral neuropathy. Tachyphylaxis is not seen during long-term administration for hypertension.[18]

Our data confirm previous preliminary studies which reported salutary hemodynamic effects of minoxidil at rest in patients with chronic congestive heart failure.[10–12] After minoxidil administration, stroke volume increased by 19% with a small but insignificant change in heart rate, accounting for a 25% increase in cardiac output. Systemic vascular resistance decreased by 35%, without significant effects on right atrial, pulmonary artery, or left ventricular filling pressure. Some patients had a substantial decrease in resting blood pressure. These effects are similar to those of other predominantly arteriolar vasodilators such as hydralazine.[6]

Improvement in stroke volume at the same left ventricular filling pressure suggests improved left ventricular performance at rest.

Our results also document beneficial hemodynamic effects of minoxidil at maximal symptom-limited exercise in this cohort of patients with severe chronic heart failure. After minoxidil treatment, there was a significant increase in cardiac output at peak exercise compared with conventional therapy alone (Fig. 1). This increase in cardiac output was accounted for by an increase in stroke volume and a smaller increase in heart rate. The effects of minoxidil and exercise on cardiac output were independent of one another.

Short-term administration of minoxidil resulted in a small but significant increase in maximal oxygen consumption because peak work load and exercise duration increased in some patients. It is possible that the improved arterial oxygen transport due to increased cardiac output allowed skeletal muscle to maintain aerobic metabolism while exercising to a higher work load. However, short-term objective improvement in work performance has not been readily demonstrated for other vasoactive drugs including hydralazine,[6,19] nitrates,[3,20] prazosin,[4,19] and phentolamine[21] despite salutary effects on exercise hemodynamics, perhaps because of a defect in muscle oxygen utilization or because of vascular shunting which prevents muscle oxygen delivery.[19,22] We expected minoxidil to have the same effects on exercise capacity and maximal oxygen uptake as observed in our other vasodilator studies.[4,6,19] Our observations require further confirmation.

One patient developed angina pectoris during short-term administration of minoxidil, while another developed a subendocardial infarction during follow-up. These complications have been observed with other vasodilators in patients with ischemic heart disease, especially during hydralazine administration.[23,24] Because we are not able to predict a priori which patients will develop ischemic side effects, we observe coronary heart disease patients very carefully after starting vasodilator therapy.

During long-term administration of minoxidil 5 patients reported subjective improvement in exercise tolerance, dyspnea, and fatigue. The major side effect of worsening dependent edema was caused by the well-recognized sodium-retaining properties of the drug[25] and was adequately controlled by careful adjustment of diuretic therapy. Even in patients who have fluid balance, we have found it prudent to increase furosemide and simultaneously start small doses of metolazone before hospital discharge. Otherwise, fluid retention may occur rapidly and prove difficult to control once it is established. Three patients who originally received minoxidil, including 2 who had massive edema, subsequently received hydralazine. The short-term hemodynamic effect was equal to that on minoxidil therapy, with no edema on outpatient follow-up study.

Minoxidil-related hypertrichosis occurs in about 80% of patients taking the drug for 1 year,[26] and is thought to be due to an increase in blood flow to the skin.[27] Hirsutism appears to be dose-related and readily reversible on discontinuation of the drug. In female patients, concomitant use of a calcium thyoglycollate depilatory may be necessary.

Pericardial effusion has been reported to occur in about 3% of hypertensive patients taking minoxidil,[17] but worsening effusion was not seen in any of our patients. Nonspecific electrocardiographic T-wave changes have been reported in up to 60% of patients with long-term minoxidil therapy (manufacturer's data, Upjohn Laboratories, Kalamazoo, Michigan). These changes may have represented left ventricular enlargement in the patients with hypertension. Similar changes did not occur during the course of the present study.

In view of our experience with chronic administration of minoxidil, we recommend that the drug be given with much caution to patients with active ischemic heart disease. After dosage titration to a hemodynamic end point, concomitant administration of furosemide and perhaps metolazone should be started in order to control edema. Frequent follow-up examination (for example, twice weekly) is necessary for the first 2 or 3 weeks of therapy in order to avoid rapid and difficult-to-control fluid retention. Female patients should be warned about the expected increase in facial hair. Although the development or worsening of pericardial effusion was not observed in our small group of patients, serial monthly echocardiography seems clinically prudent at this time.

Acknowledgment

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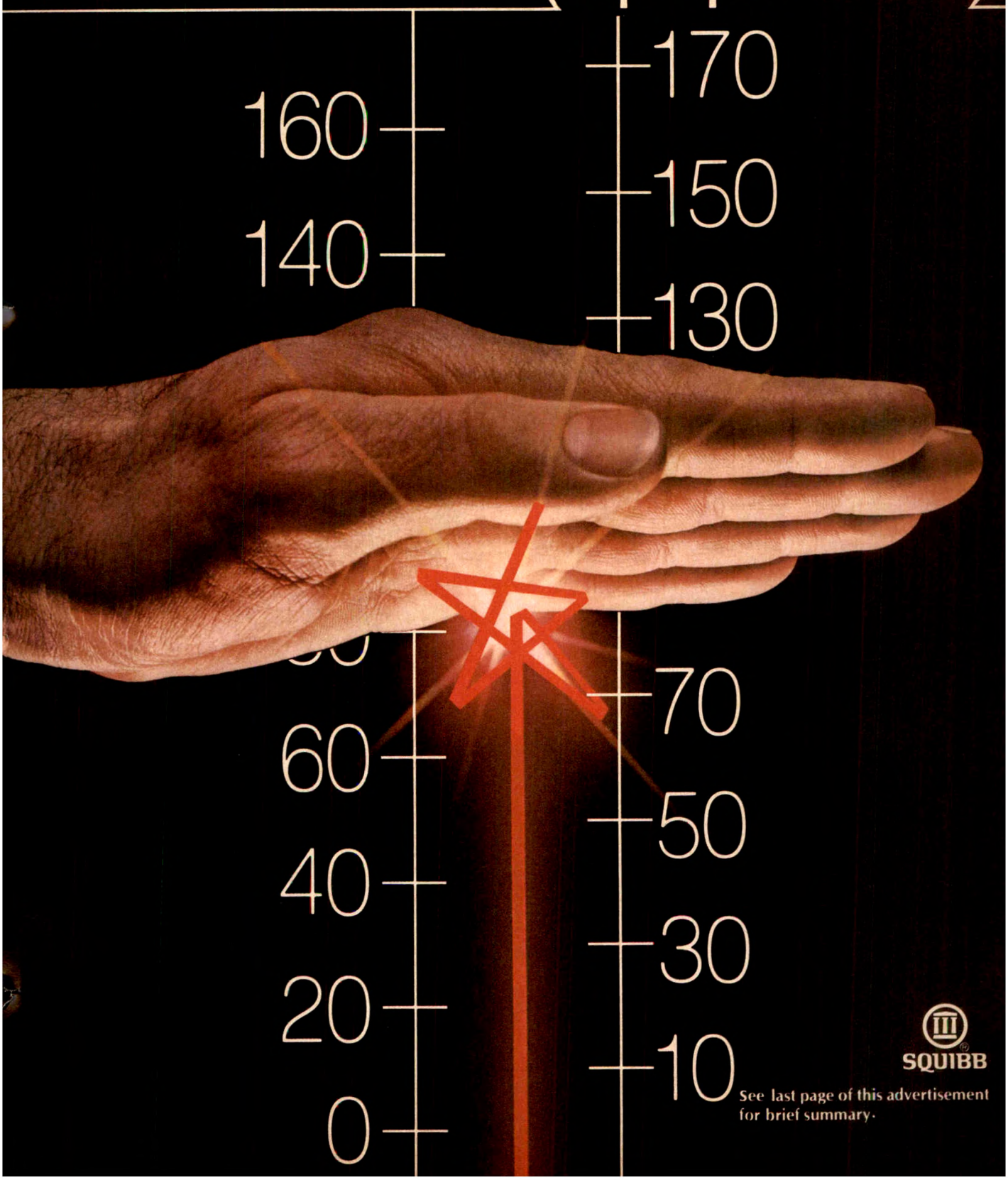

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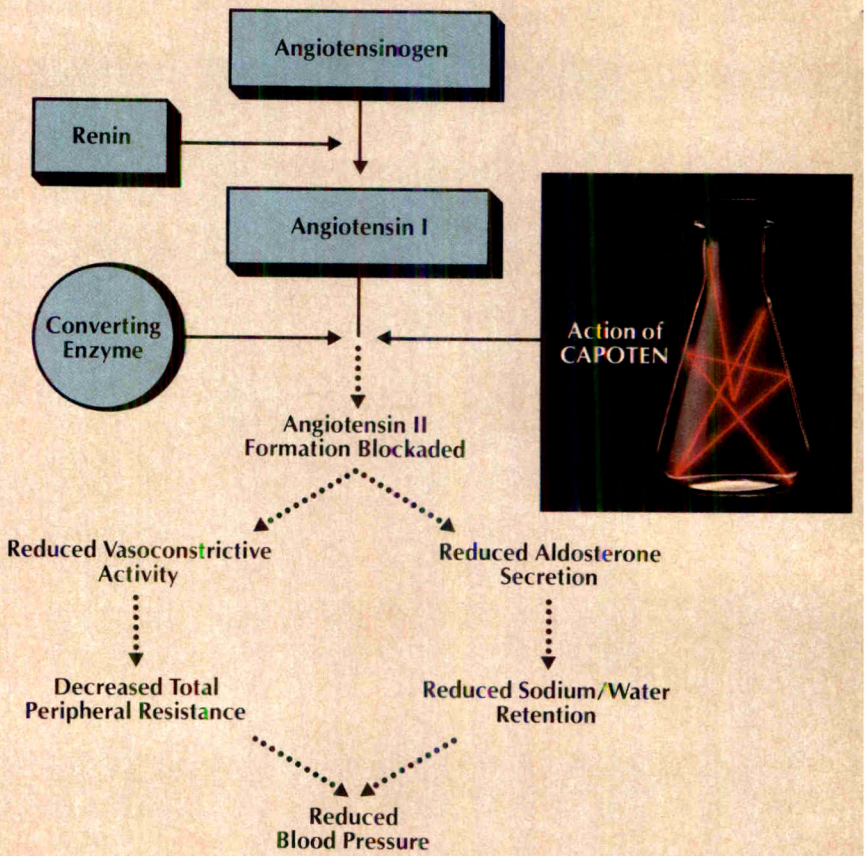

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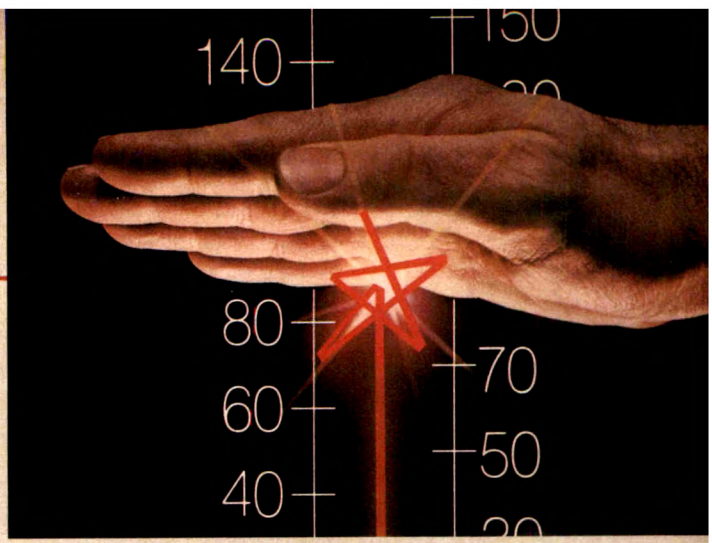

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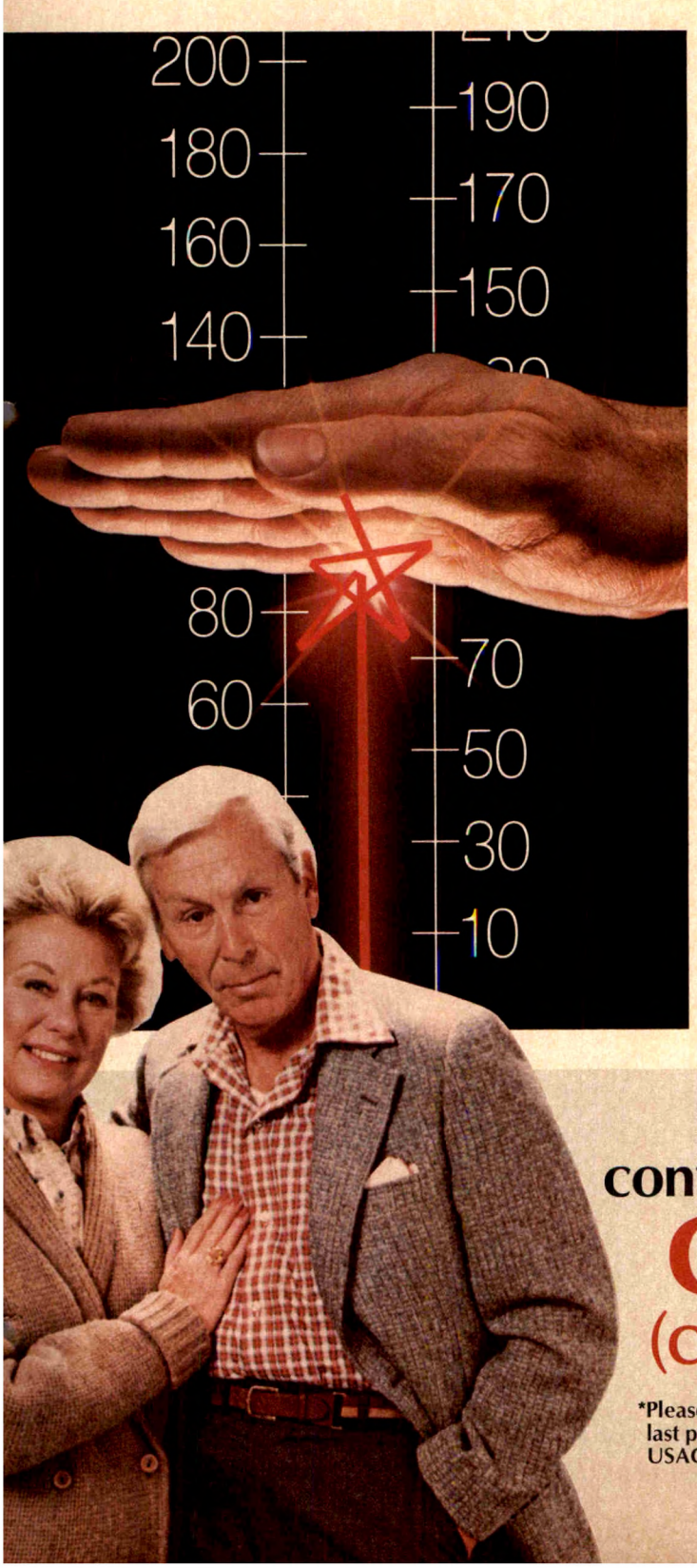

Effective blood pressure control

▶ Routine monitoring procedures are recommended because serious side effects (neutropenia/agranulocytosis, proteinuria) have been associated with CAPOTEN.*

▶ Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.

▶ Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.

▶ Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.

▶ The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

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DESCRIPTION: Capoten (captopril) is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for converting angiotensin I to angiotensin II.

INDICATIONS: Because serious adverse effects have been reported (see WARNINGS), Capoten is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects. Usually, multidrug regimens include combinations of a diuretic, a sympathetic nervous system-active agent (such as a beta-blocker) and a vasodilator.

Capoten (captopril) is effective alone, but in the population described above, it should usually be used in combination with a thiazide-type diuretic. The blood pressure lowering effects of captopril and thiazides appear to be additive.

WARNINGS: Proteinuria—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. Existence of prior renal disease increased the likelihood of development of proteinuria. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued, but some patients had persistent proteinuria. The BUN and creatinine were seldom altered in the proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related; this is uncertain since patients were not biopsied prior to treatment and membranous glomerulopathy may be associated with hypertension in absence of captopril therapy. Since most cases of proteinuria occurred by the 8th month of captopril therapy, patients on captopril should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis—Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller, and it is sufficient in these patients to have white blood cell counts every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in severely salt/volume depleted persons such as those treated vigorously with diuretics, e.g., patients with severe congestive heart failure (see PRECAUTIONS [Drug Interactions]).

PRECAUTIONS: General: *Impaired Renal Function*—Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible (see DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]). *Surgery/Anesthesia*—During major surgery or anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release; if hypotension occurs and is considered due to this mechanism, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy*—A precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretic therapy and those on severe dietary salt restriction or dialysis. The possibility of hypotensive effects can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose. If hypotension occurs, place the patient in a supine position and, if necessary, administer an I.V. infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Since captopril decreases aldosterone production, elevation of serum potassium may occur. Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. If the patient has received spironolactone at any time up to several months prior to captopril therapy, determine the serum potassium frequently since the effect of spironolactone persists.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential.

Animal Toxicology: Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and variation of retinal blood vessels. Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses 50 to 150 times the maximum recommended human dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8 to 30 times MRHD. The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8 to 30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 and 30 times MRHD and thrombocytopenia at 30 times MRHD. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacrificed in a moribund condition in the 1-year study. However, in the 47-week study at a dose 30 times MRHD, bone marrow suppression was found to be reversible upon continued drug administration. Captopril caused hyperplasia of the juxtaglomerular apparatus of the kidneys at doses 7 to 200 times the MRHD in rats and mice, at 20 to 60 times MRHD in monkeys, and at 30 times the MRHD in dogs. Gastric erosions/ulcerations were increased in incidence at 20 and 200 times MRHD in male rats and at 30 and 65 times MRHD in dogs and monkeys, respectively. Rabbits developed gastric and intestinal ulcers when given oral doses about 30 times MRHD for only 5 to 7 days. In the two-year rat study, irreversible and progressive variations in the caliber of retinal vessels (focal sacculations and constrictions) occurred at all dose levels (7 to 200 times MRHD) in a dose-related fashion. The effect was first observed in the 88th week of dosing, with a progressively increased incidence thereafter, even after cessation of dosing.

Pregnancy: Category C—Captopril was embryocidal in rabbits when given in doses 2 to 6 times (on a mg/kg basis) the maximum recommended human dose. The marked embryocidal effect in rabbits was most probably due to the particularly marked decrease in blood pressure caused by the drug in this species. Captopril given to pregnant rats at 400 times the recommended human dose continuously during gestation and lactation reduced neonatal survival. No teratogenic effects (malformations) have been seen at large doses of captopril in hamsters, rats, and rabbits.

There are no adequate and well-controlled studies in pregnant women. Captopril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Concentrations of captopril in human milk are about 1% of those in maternal blood. The effect of low levels of captopril on the nursing infant has not been determined. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age with secondary hypertension and varying degrees of renal insufficiency. Dosage on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal—One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients but relationship to drug use is uncertain.

Hematologic—Neutropenia/agranulocytosis (probably drug related) occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic—Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the first 4 weeks of therapy. The rash is usually mild and disappears within a few days of dosage reduction, short-term treatment with an antihistaminic agent, and/or discontinuing therapy; remission may occur even if captopril is continued. Pruritus, without rash, in about 2 of 100 patients. Between 7 and 10% of patients with skin rash have shown an eosinophilia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension in about 2 of 100 patients. See PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 100 patients.

Dysgeusia—About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Weight loss may be associated with the loss of taste. Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although a causal relationship has been established. A single case of hepatocellular injury with secondary cholestasis has been reported in association with captopril use. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. Dosage must be individualized.

Give consideration to recent antihypertensive drug therapy, extent of blood pressure elevation, salt restriction, and other circumstances before initiating therapy. If possible, discontinue the patient's previous antihypertensive drug regimen for one week before starting captopril. Initial dose of CAPOTEN (captopril) is 25 mg t.i.d. If satisfactory blood pressure reduction is not achieved after 1 or 2 weeks, dose may be increased to 50 mg t.i.d. If the blood pressure has not been satisfactorily controlled after another 1 to 2 weeks, add a modest dose of a thiazide-type diuretic (e.g., hydrochlorothiazide, 25 mg daily). The diuretic dose may be increased at 1- to 2-week intervals until its highest usual antihypertensive dose is reached. If further blood pressure reduction is required, CAPOTEN (captopril) may be increased to 100 mg t.i.d. and then, if necessary, to 150 mg t.i.d. (while continuing the diuretic). The usual dose range is 25 to 150 mg t.i.d. A maximum daily dose of 450 mg CAPOTEN (captopril) should not be exceeded.

For patients with accelerated or malignant hypertension, when temporary discontinuation of current antihypertensive therapy is not practical, or when prompt titration to more normotensive blood pressure levels is indicated, current antihypertensive medication may be stopped and CAPOTEN (captopril) dosage promptly initiated at 25 mg t.i.d., under close medical supervision. The daily dose of CAPOTEN (captopril) may be increased every 24 hours until a satisfactory blood pressure response is obtained or the maximum captopril dose is reached. In this regimen, addition of a more potent diuretic, e.g., furosemide, may also be indicated. Beta-blockers may also be used in conjunction with captopril therapy (see PRECAUTIONS [Drug Interactions]), but the effects of the 2 drugs are less than additive.

Dosage Adjustment in Renal Impairment—Because CAPOTEN (captopril) is excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. These patients will take longer to reach steady-state captopril levels and will reach higher steady-state captopril levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent doses. Accordingly, for patients with significant renal impairment, initial daily dosage of CAPOTEN (captopril) should be reduced, and smaller increments utilized for titration, which should be quite slow (1- to 2-week intervals). After desired therapeutic effect has been achieved, dose should be slowly back-titrated to determine minimal effective dose. When concomitant diuretic therapy is required, a loop diuretic (e.g., furosemide), rather than a thiazide diuretic, is preferred in patients with severe renal impairment.

For full prescribing information, consult package insert.

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

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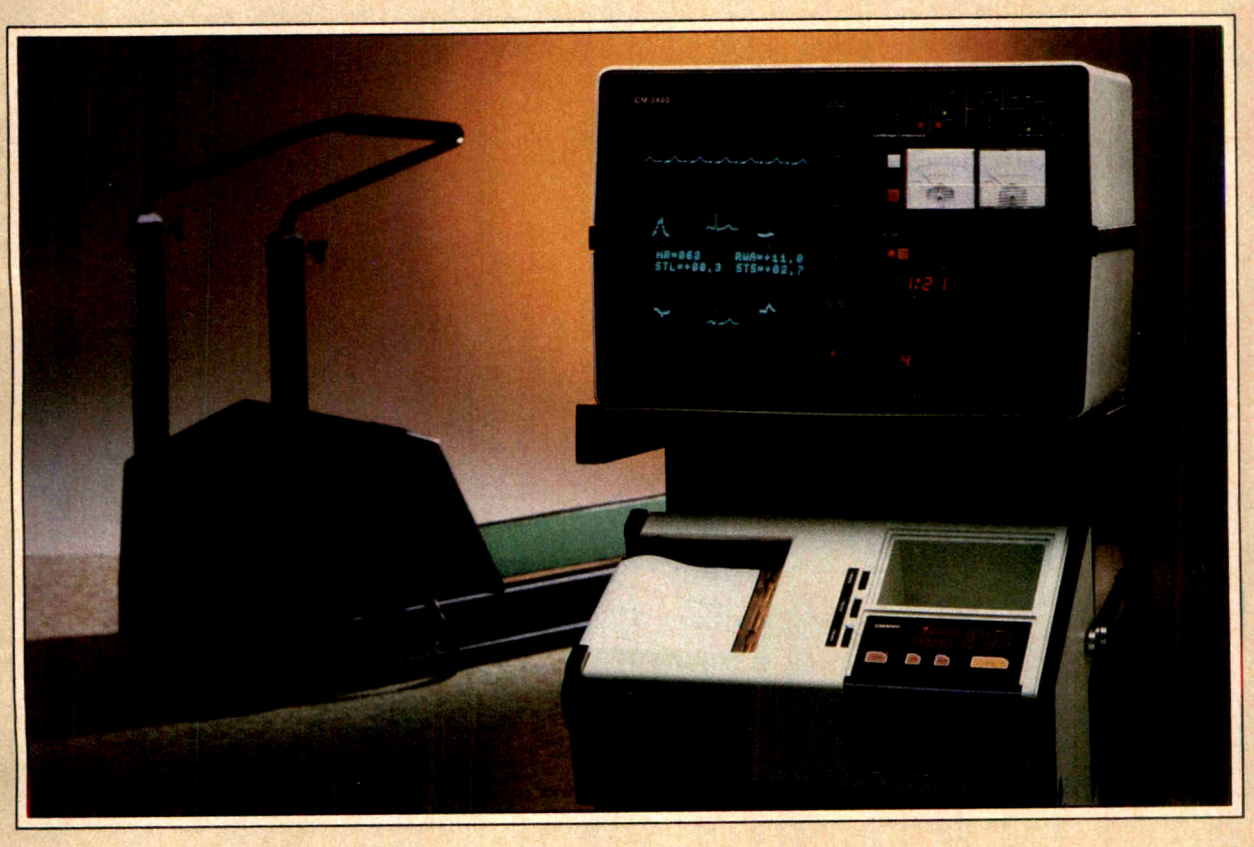

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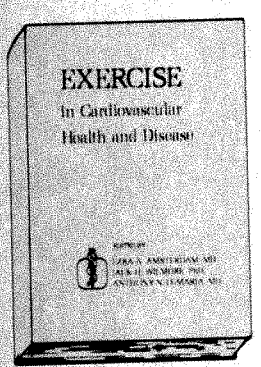

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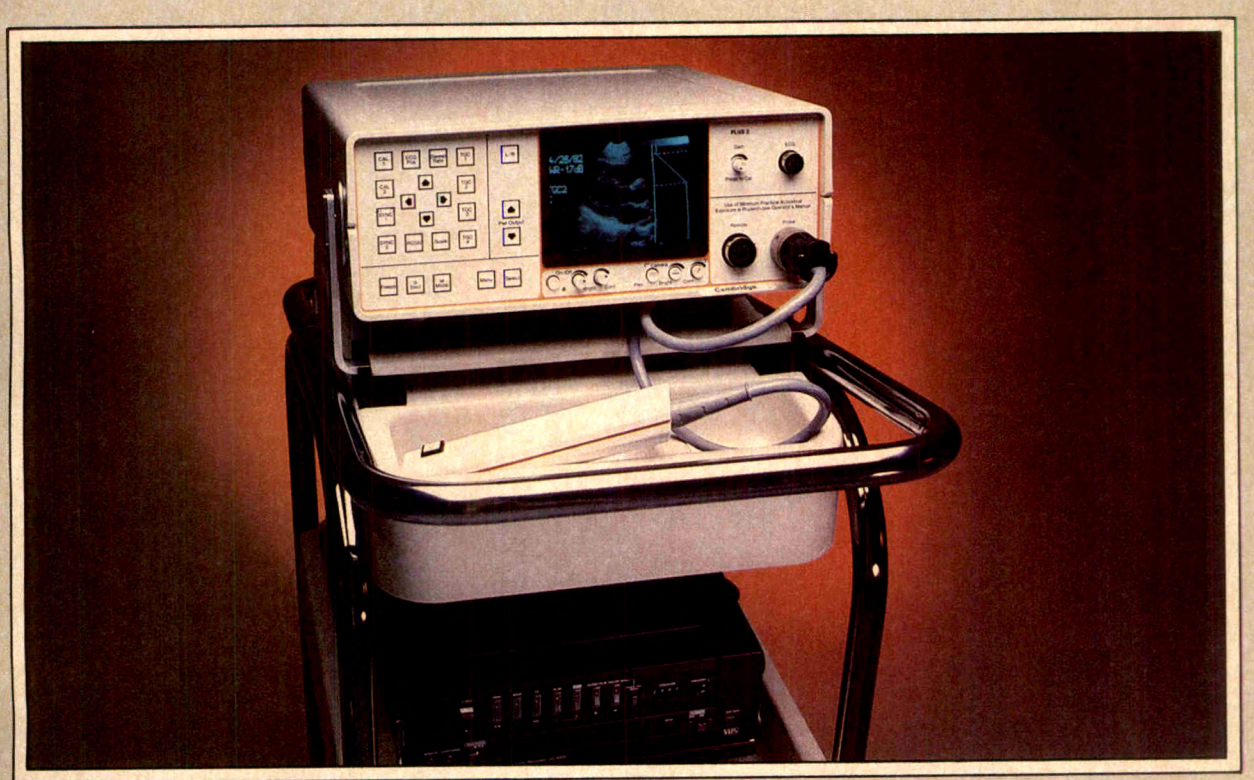

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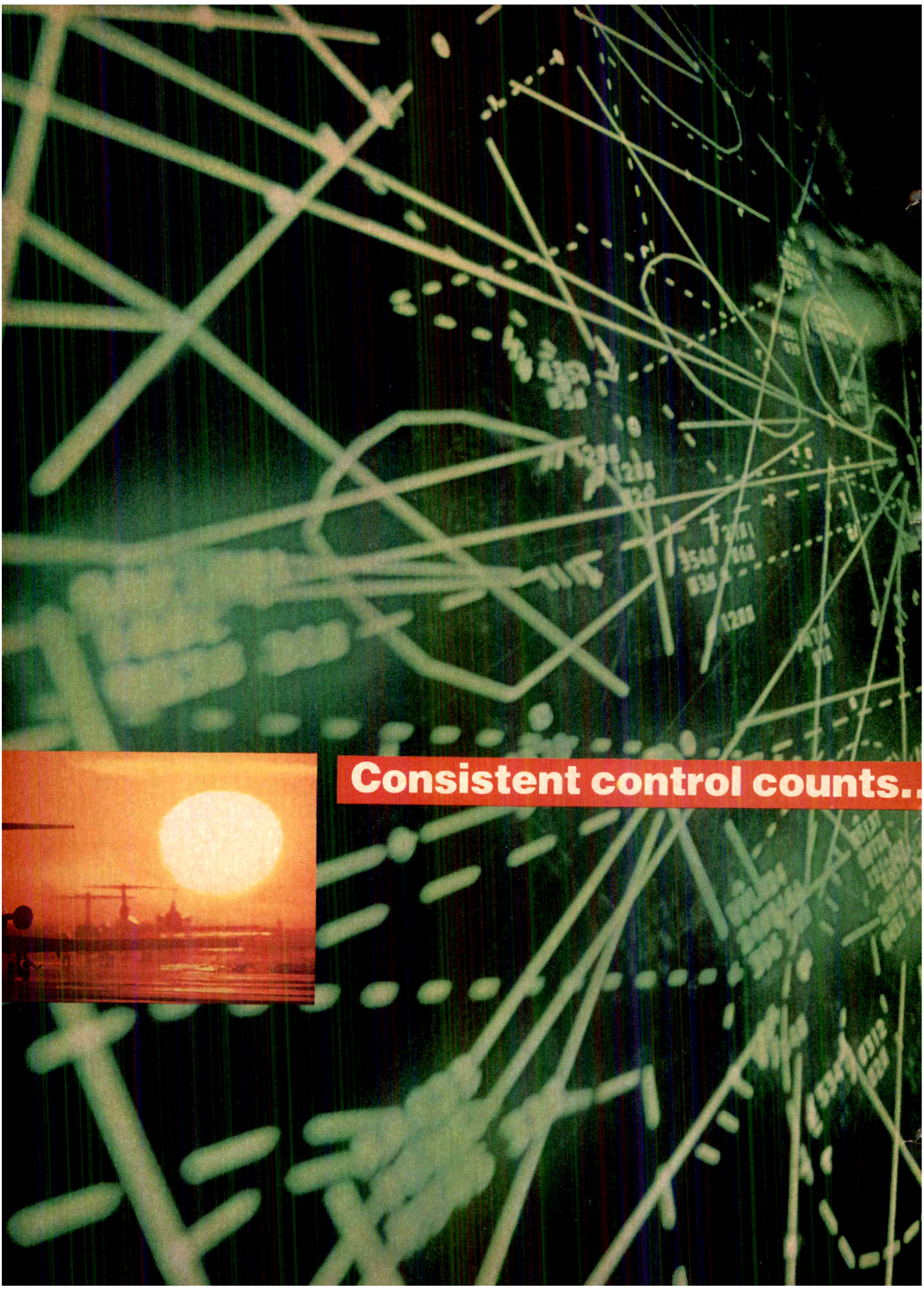
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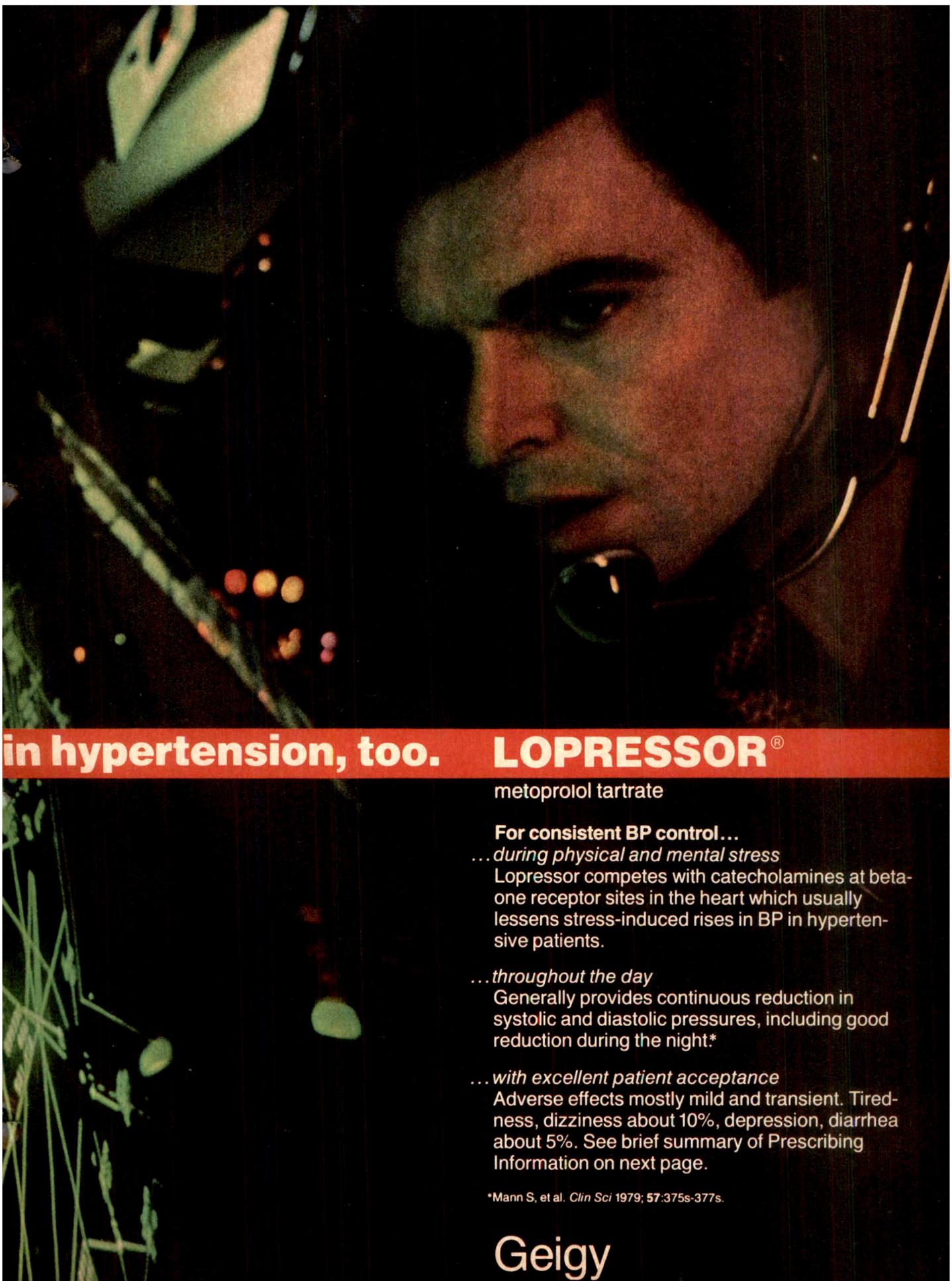

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Generally provides continuous reduction in systolic and diastolic pressures, including good reduction during the night.*

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Adverse effects mostly mild and transient. Tiredness, dizziness about 10%, depression, diarrhea about 5%. See brief summary of Prescribing Information on next page.

*Mann S, et al. *Clin Sci* 1979; **57**:375s-377s.

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Lopressor®
metoprolol tartrate

An antihypertensive beta-blocking agent	Tablets of 50 mg Tablets of 100 mg

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.
Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).
Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.
In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.
Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.
Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**
Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.
Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.
Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.
Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.
Precautions Impaired Hepatic or Renal Function: The drug should be used with caution in patients with impaired hepatic or renal function.
Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.
Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.
Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.
Usage in Children: Safety and effectiveness in children have not been established.
Adverse Reactions Most adverse effects have been mild and transient.
Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.
Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**
Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**
Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.
Allergic: Pruritus has occurred in less than 1 of 100 patients.
Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients. The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.
Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.
Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.
Cardiovascular: Intensification of AV block (see **Contraindications**).
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.
Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.
Miscellaneous: Reversible alopecia.
Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.
Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta, selectivity diminishes as dosage of Lopressor is increased.
This drug should be stored at controlled room temperature and protected from moisture.
How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.
Store at controlled room temperature and protect from moisture.
Dispense in tight, light-resistant container (USP).

C80-82 (12/80)

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Coronary Hemodynamic Effects of Angiotensin Inhibition By Captopril and Teprotide in Patients With Congestive Heart Failure

JONATHAN L. HALPERIN, MD, DAVID P. FAXON, MD, MARK A. CREAGER, MD, THEODORE A. BASS, MD, CAROLINE D. MELIDOSSIAN, RN, HARALAMBOS GAVRAS, MD, and THOMAS J. RYAN, MD

The coronary hemodynamic effects of vasodilator therapy with angiotensin-converting enzyme inhibitors (captopril and teprotide) were studied in 11 patients with ischemic heart disease and severe congestive heart failure (CHF). Over 2 hours, systemic vascular resistance was reduced from 2,408 ± 240 to 1,715 ± 170 dynes·s·cm^{-5} ($p < 0.001$), and cardiac output improved 18%, resulting in lower arterial pressure (101 ± 8 to 86 ± 5 mm Hg, $p < 0.001$) and left ventricular filling pressure (30 ± 2 to 21 ± 2 mm Hg, $p < 0.001$). Coronary sinus thermodilution blood flow paralleled perfusion pressure but did not significantly vary overall (160 ± 20 to 133 ± 12 ml/min, difference not significant [NS]). Coronary vascular resistance was unchanged. Although the left ventricular stroke work index rose slightly (37.7 ± 8.8 to 41.3 ± 7.9 g·m/m^2, $p < 0.05$), there was no change in the coronary arteriovenous oxygen content difference (10.8 ± 1.0 to 10.4 ± 1.0 ml/100 ml, NS) or calculated myocardial oxygen consumption (16.4 ± 1.9 to 13.9 ± 1.6 ml/min, NS). The heart rate-systolic blood pressure product declined significantly during this period (8,824 ± 703 to 7,087 ± 514 beats·mm Hg, $p < 0.02$); this relief of cardiac effort was a function of the pretreatment plasma renin activity. A derived index of external myocardial efficiency improved 37% (19 ± 3 to 26 ± 6, $p < 0.05$), reflecting greater left ventricular work without increased oxygen demand.

Enhancement of myocardial performance after converting enzyme inhibition appears dependent on reduction of angiotensin-mediated ventricular afterload and preload. The lack of coronary vasomotor effects in patients with advanced ischemic cardiomyopathy may reflect limited coronary vascular reserve. Improvement of heart failure in these patients developed without evidence of myocardial ischemia, since balance was maintained between oxygen supply and demand.

Angiotensin-converting enzyme inhibitors lessen systemic vascular resistance and improve cardiac function in patients with CHF, yet the effects of this form of therapy upon cardiac perfusion and metabolism are mainly unknown.[1–5] Under normal circumstances resistance to coronary flow is regulated mainly by myocardial oxygen requirements, but coronary vessels also respond to stimulation of adrenergic and cholinergic receptors and to humoral mechanisms such as the renin-angiotensin system.[6,7] Obstructive coronary heart disease and ventricular dysfunction further influence the distribution of blood flow within the cardiac musculature. Consequently, the responses of the coronary circulation to ischemic myocardial failure are particularly difficult to define.

We examined coronary hemodynamics and myocardial energetics in a group of patients with severe CHF due to coronary heart disease during therapy with 2 distinct converting enzyme inhibitors (captopril and

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TABLE I Systemic Hemodynamic and Plasma Renin Data Before and After Angiotensin Inhibition

Case	Period	PRA (ng/ml/h)	HR (beats/min)	BP (mm Hg)	RA (mm Hg)	PCW (mm Hg)	CI (liters/min/m^2)	LVSWI (g·m/m^2)
1	Before	22	84	80	19	32	0.98	12.0
	After	39	79	70	12	19	1.42	18.2
2	Before	68	92	138	2	29	2.40	69.4
	After	107	71	83	1	7	2.61	74.1
3	Before	7	74	90	7	20	2.64	61.0
	After	14	68	76	8	16	2.66	58.1
4	Before	5	102	107	18	42	1.30	30.9
	After	8	100	99	15	33	1.51	37.3
5	Before	4	83	91	22	34	1.29	19.3
	After	9	77	81	19	26	1.87	24.2
6	Before	18	78	81	7	23	1.70	26.3
	After	43	85	80	7	21	2.01	27.2
7	Before	39	88	79	14	33	1.25	15.8
	After	66	80	72	15	25	1.63	22.3
8	Before	13	113	80	18	23	1.82	17.0
	After	38	109	63	18	18	2.04	17.8
9	Before	7	75	122	23	39	1.09	20.0
	After	13	72	111	19	30	1.48	29.0
10	Before	4	93	91	8	28	2.67	37.0
	After	6	90	84	6	23	3.34	47.0
11	Before	20	84	150	10	26	3.24	106.0
	After	89	84	122	6	12	3.55	99.0
Mean	Before	19 ± 6	88 ± 4	101 ± 8	13 ± 2	30 ± 2	1.85 ± 0.23	37.7 ± 8.8
±SEM	After	39 ± 11	83 ± 4	86 ± 5	11 ± 2	21 ± 2	2.19 ± 0.23	41.3 ± 7.9
p	...	<0.01	<0.05	<0.01	NS	<0.001	<0.001	<0.05

BP = mean arterial blood pressure; CI = cardiac index; HR = heart rate; LVSWI = left ventricular stroke-work index; PCW = mean pulmonary capillary wedge pressure; PRA = plasma renin activity; RA = mean right atrial pressure.

teprotide). The purpose of the study was to help define the impact of the renin-angiotensin system on coronary vascular tone in patients with ischemic cardiomyopathy and shed light on the myocardial energetic consequences of vasodilator therapy in this disorder.

Methods

Study patients: Eleven patients with signs and symptoms of severe CHF in New York Heart Association functional classes III and IV were studied. All had angiographic evidence of advanced multivessel coronary artery disease or documented previous myocardial infarction. Seven of these patients had angina pectoris. None had had clinically apparent infarction within 6 months of study or had predominant valvular disease. Eight patients were male and 3 were female; their ages ranged from 52 to 75 years (average 63). The duration of cardiac failure ranged from 5 months to 14 years (average 3.7 years).

Catheterization procedures: The experiment had the approval of the Institutional Review Board for Human Research, and each patient gave informed consent. Subjects were maintained in the hospital on an 86 mEq/day sodium diet for 3 days before study. Digitalis, diuretics, and all medications other than clinically necessary antiarrhythmic agents were withheld for 24 hours before the hemodynamic studies. With patients in the recumbent, postabsorptive state and without premedication, 18-g polyethylene radial arterial cannulas were placed. Each patient underwent right heart catheterization with a 7Fr Swan-Ganz catheter (Instrumentation Laboratories), and coronary sinus catheterization was performed with an 8Fr Ganz thermodilution catheter (USCI Division, C.R. Bard). These catheters were introduced through antecubital veins and positioned using fluoroscopy. Periodic injections of small volumes of radioopaque contrast medium confirmed the location of the coronary sinus catheter during the studies. Pressures were measured using Bentley model 508 strain-gauge transducers and recorded on a direct-writing Hewlett-Packard multigraph. Mean pressures were obtained by electronic integration with zero-reference at the level of the mid-axillary line. Heart rate was determined from the simultaneous electrocardiographic signal. Cardiac output was quantified by thermodilution, using an Instrumentation Laboratories model 601 cardiac output computer and averaging at least 3 replicate determinations varying less than 10%. Coronary sinus blood flow was measured by the thermodilution technique, using a Wheatstone bridge (Wilton-Webster Laboratories, Altadena, California) and recorded as described by Ganz et al.[8] Whole blood oxygen saturation was measured with a Beckman spectrophotometer according to the method of Gordy and Drabkin,[9] and corrected for the oxygen-carrying capacity of hemoglobin to derive volumetric oxygen content. Lactate content was determined by the method of Friedland and Dietrich.[10] Plasma renin activity was quantified in systemic venous blood by radioimmunoassay of angiotensin I generation.[11]

Measurements before and after captopril or teprotide: Systemic hemodynamic data were collected until 3 successive determinations 15 minutes apart demonstrated homeostasis. Coronary sinus blood flow measurements were made simultaneously with measurements of cardiac output, systemic blood pressure, pulmonary capillary wedge pressure, right atrial pressure, and heart rate. Coronary sinus and arterial blood were sampled simultaneously for determinations of oxygen and lactate contents immediately after each measurement of coronary sinus flow. Venous blood was taken for plasma renin activity and norepinephrine concentration just before drug administration. Five patients were given teprotide, 1 mg/kg as an intravenous injection, and 6 patients received captopril, 100 mg orally (Squibb Institute of Medical Research, Princeton, New Jersey). Hemodynamic data were collected at 15, 30, 45, and 60 minutes thereafter in patients given teprotide, and at 30, 60, 90, and 120 minutes after captopril administration. Blood for oxygen content and lactate

TABLE II Coronary Hemodynamic and Myocardial Energetic Data Before and After Angiotensin Inhibition

Case	Period	CSBF (ml/min)	CVR (dynes·s·cm^{-5})	AVO_2 df (vol/100 ml)	MVO_2 (ml/min)	RPP (mm Hg·beat)	EME (%)
1	Before	134	36.4	11.5	15.4	6,720	9.5
	After	107	42.8	11.0	11.8	5,530	15.1
2	Before	308	35.3	10.0	30.8	12,696	20.0
	After	171	39.3	8.8	15.0	5,893	32.1
3	Before	158	42.0	8.9	14.1	6,660	28.7
	After	143	37.6	8.4	12.0	5,168	28.4
4	Before	110	64.7	13.9	15.3	10,914	13.9
	After	103	65.8	13.2	13.6	9,900	17.4
5	Before	165	33.4	11.4	18.8	7,553	13.8
	After	171	28.8	13.0	22.2	6,237	13.4
6	Before	107	55.3	12.9	13.8	6,318	16.5
	After	104	55.9	13.7	14.2	6,800	18.4
7	Before	105	49.5	11.4	12.0	6,952	14.0
	After	126	36.4	11.0	13.9	5,760	13.8
8	Before	142	34.9	8.8	12.5	9,040	12.8
	After	107	35.1	8.1	7.0	6,867	25.4
9	Before	113	70.1	16.9	19.1	9,150	11.4
	After	114	65.3	14.3	16.1	7,992	16.7
10	Before	255	26.0	8.3	21.1	8,463	18.4
	After	220	29.9	9.7	19.0	7,560	25.0
11	Before	168	66.7	4.3	17.0	12,600	45.5
	After	102	96.0	3.6	9.0	10,250	76.8
Mean ±SEM	Before	160 ± 20	46.8 ± 4.6	10.8 ± 1.0	16.4 ± 1.9	8,824 ± 703	18.6 ± 3.1
	After	133 ± 12	48.4 ± 6.2	10.4 ± 1.0	13.9 ± 1.6	7,087 ± 514	25.7 ± 5.5
p	...	NS	NS	NS	NS	<0.02	<0.05

AVO_2 df = coronary arteriovenous oxygen content difference; CSBF = coronary sinus blood flow; CVR = coronary vascular resistance; EME = external myocardial efficiency; MVO_2 = myocardial oxygen consumption; RPP = rate-pressure index.

concentration was drawn at the time of hemodynamic measurements, and blood for plasma renin activity was taken 60 and 120 minutes after administration of teprotide and captopril, respectively.

Hemodynamic indexes were derived from pressure, flow, and oxygen content values according to the formulas presented in the Appendix. Coronary sinus flow was derived from the change in the temperature of coronary sinus blood during infusion of 5% dextrose in water at 20°C at a rate of 50 ml/min, as detected by thermistors mounted on the coronary sinus catheter. The relative densities and specific heats of coronary sinus blood and indicator solution of dextrose required a constant correction factor of 1.08. Total coronary resistance was calculated as the ratio of arteriovenous driving pressure to coronary sinus flow. Myocardial oxygen consumption was evaluated as the product of blood flow and oxygen extraction. External myocardial efficiency was calculated to express the amount of cardiac work performed per unit of oxygen consumed.

Statistical analysis: Systemic hemodynamic measurements were averaged over the control period and over the hour of peak systemic vasodilatory effect, determined from the change in systemic vascular resistance. Data before and after converting enzyme inhibition were compared and evaluated by the paired Student's *t* test and expressed as mean ± standard error of the mean. The Pearson product-moment correlation coefficient was computed for effects along selected parameters. Statistical significance was accepted at the 95% confidence level ($p < 0.05$).

Results

Plasma renin activity: In all 11 cases, chronic CHF was attributed to coronary heart disease. The population remained heterogeneous with respect to basal plasma renin activities, which ranged from 3.9 to 68.0 ng/ml/h. Renin activity increased in all cases, but increased the most in patients with the highest baseline levels. The individual and group results are presented in Tables I and II.

Systemic vasodilatation: Pretreatment plasma renin activity predicted the degree of systemic vasodilatation after drug administration ($r = -0.604$; $p < 0.05$). Systemic vascular resistance was consistently lower after converting enzyme inhibition than during the control period. On average, the mean arterial pressure decreased 15 percent as the cardiac index improved 18 percent. Mean pulmonary capillary wedge pressure fell 30 percent, but generally remained well above the normal range after treatment with angiotensin inhibitors. Mean right atrial pressure did not fall significantly

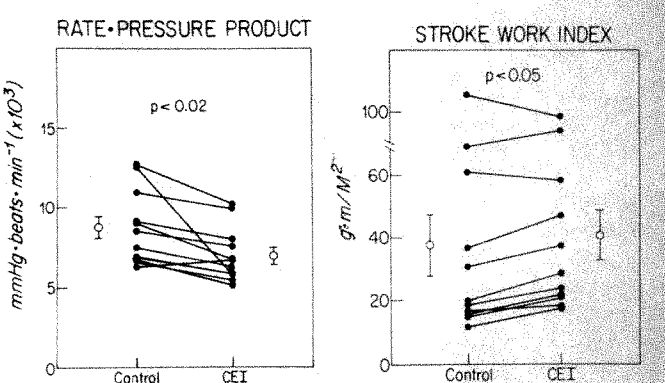

FIGURE 1. Left ventricular stroke-work index (**right**) and heart rate-systolic blood pressure product (**left**) in each patient before and after converting enzyme inhibition (CEI) (mean ± standard error of the mean [SEM]).

during short-term observation. The heart rate slowed slightly. The index of left ventricular stroke work increased in 9 of 11 patients (Fig. 1). Simultaneously, the product of the heart rate and systolic blood pressure (an index of cardiac effort) declined an average of 19 percent. The change in rate-pressure product reflected the decrease in systemic vascular resistance and was related to baseline plasma renin activity ($r = -0.769$; $p < 0.01$).

Coronary hemodynamics: During the period of drug action, there was no significant change in coronary sinus blood flow (Fig. 2). In 8 patients, flow decreased; the reduction in coronary venous flow was related to the decrease in perfusion pressure ($r = 0.750$; $p < 0.01$). Calculated total coronary resistance was also unchanged despite substantial systemic vasodilatation. Changes in coronary sinus blood flow paralleled reductions in blood pressure. The transmyocardial diastolic pressure gradient (calculated as the difference between diastolic systemic arterial pressure and pulmonary capillary wedge pressure) was unchanged during converting enzyme inhibition.

Myocardial function and metabolism: Coronary sinus blood oxygen content initially averaged 3.9 ± 0.2 ml/100 ml. There was no shift in the coronary arteriovenous oxygen difference after administration of the converting enzyme inhibitors. Myocardial oxygen consumption was not changed significantly (16.4 ± 1.9 to 13.9 ± 1.6 ml/min, $p < 0.20$). Values decreased in 8 subjects, however, and parallelled the change in the rate- pressure product ($r = 0.613$; $p < 0.05$). Enhanced stroke work without change in oxygen uptake indicates improvement in the metabolic efficiency of the heart (Fig. 3). The calculated index of external myocardial efficiency improved from 19 ± 3 to 26 ± 6% ($p < 0.05$), and substantial increases occurred in most patients. In accord with these findings, no significant increment in myocardial lactate production developed even at reduced rates of myocardial perfusion (20 ± 13 to 13 ± 13%, $p < 0.50$).

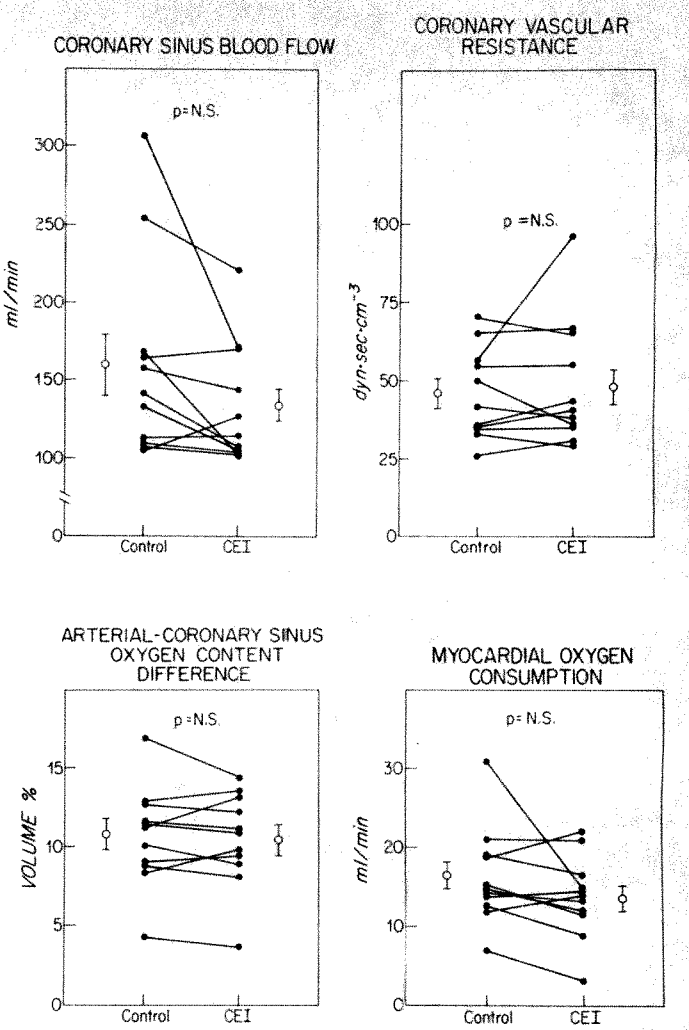

FIGURE 2. Coronary hemodynamic response to angiotensin inhibition (CEI). Coronary sinus blood flow, coronary vascular resistance, coronary arteriovenous oxygen content difference, and myocardial oxygen consumption are given for each subject, along with the mean ± SEM.

Discussion

Role of renin-angiotensin system: In patients with CHF, regional tissue perfusion is regulated selectively by a variety of vasoconstrictor mechanisms. Collectively, systemic vasoconstriction generates resistance to left ventricular ejection, increasing intramyocardial tension during systole. The afterload imposed by aortic impedance represents a principal determinant of myocardial oxygen consumption. In the patients with chronic coronary heart disease described herein, the decrease in peripheral resistance during therapy with angiotensin converting enzyme inhibitors was related to the baseline plasma renin activity. Inhibition of the vasoconstrictor properties of angiotensin II is thus implicated, although other neurohumoral actions may contribute to the effects of teprotide and captopril.[12] Both angiotensin I and angiotensin II produce coronary vasoconstriction in anesthetized dogs. The increase in coronary vascular resistance after administration of angiotensin I is inhibited by teprotide.[13] In renin-stimulated canine models, converting enzyme inhibitors increase coronary blood flow.[14,15] Recently, we demonstrated that converting enzyme inhibition with teprotide increases coronary sinus blood flow in normal human subjects without suppressed plasma renin activities.[16] A role for the renin-angiotensin system in regulating coronary vasomotor activity is suggested by these observations.

Effect of angiotensin inhibition on coronary hemodynamics: In our patients with advanced ischemic heart disease, pretreatment values of coronary sinus blood flow ranged nearly threefold. There was no net change in the coronary sinus flow measurements after angiotensin inhibition. In several cases, however, flow rates diminished, and blood pressure decreased the most in these cases. It would seem from the constancy of the calculated coronary resistance that no vasodilatation or vasoconstriction developed in the coronary bed. This relative coronary vasomotor inactivity may reflect the limitation of coronary vascular reserve in

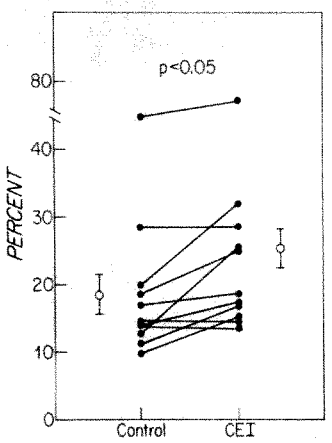

FIGURE 3. Calculated index of external myocardial efficiency for each patient before and after converting enzyme inhibition (CEI) (mean ± SEM).

ischemic heart disease.[17] Resistance to myocardial blood flow derives from several components: (1) the fixed resistance imposed by the vascular walls and blood constituents; (2) the cyclic effects of intramyocardial compression; and (3) the regulatory resistance due to constriction of arterioles.[18] In the patients we studied, resistance at the level of the epicardial coronary arteries was probably high and relatively fixed as a result of obstructive atherosclerotic disease. In response to elevated basal resistance, compensatory arteriolar vasodilatation may develop at the expense of coronary vascular reserve. Extravascular coronary resistance varies directly with changes in intramyocardial compressive forces, which are related to afterload, preload, and contractility. Flow through coronary collateral channels is subject to other factors, yet perfusion pressure is probably critical. The fact that calculated coronary resistance was constant in our study implies a balance between palliative effects on wall tension and reduced arteriovenous driving pressure across the coronary vascular bed. Excessive ventricular afterload and preload may provide the dominant metabolic stimulus to the preservation of coronary blood flow in patients with heart failure due to coronary heart disease. We have not measured total myocardial perfusion, and our results are subject to the limitations of the coronary sinus thermodilution technique.[8] Even if total blood flow were unchanged, angiotensin inhibition might modify its distribution within cardiac muscle toward or away from ischemic zones.

Effect on myocardial oxygen consumption: The coronary circulation is subject to autoregulation by which resistance to coronary blood flow is dictated predominantly by myocardial oxygen demands.[19] Even under physiologic conditions, myocardial oxygen extraction is high, so the oxygen saturation of coronary venous blood normally averages only 20 to 30 percent. The efficiency with which oxygen is utilized normally remains relatively fixed, and increases in myocardial oxygen requirements must therefore be met by corresponding increments in coronary blood flow. Factors which determine myocardial oxygen requirements, particularly ventricular wall tension (a product of intramyocardial pressure and chamber dimensions), heart rate, and the contractile state of the myocardium, ultimately modulate coronary blood flow. Very low values of coronary venous oxygen content were recorded in our patients with ischemic cardiomyopathy, indicating nearly maximum myocardial extraction of the arterial oxygen content. Calculated myocardial oxygen consumption was not significantly lowered during vasodilator therapy with angiotensin-converting enzyme inhibitors despite the decrease in rate-pressure product. Since left ventricular filling pressure and systemic vascular resistance decreased, it seems reasonable that both chamber distention and outlet impedance were reduced. An inotropic action of teprotide or captopril cannot be excluded, and this could explain the discrepancy between the rate-pressure product and myocardial oxygen consumption. In addition, this estimate of oxygen consumption conceals regional differences in oxygen employment within the myocardium.

Effect on myocardial efficiency: Clinical implications: While myocardial oxygen consumption did not change, relief of congestive heart failure allowed greater stroke work to be generated from a fixed quantity of oxygen. The percent change in external myocardial efficiency was a function of that in plasma renin activity after converting enzyme inhibition. This relation between efficient cardiac oxygen utilization and the renin-angiotensin system may be based on reduction of ventricular afterload and preload. The clinical implication is that heart failure may be improved by angiotensin inhibition without adversely affecting myocardial energetics in patients with coronary heart disease. Accordingly, our patients seem to have enjoyed functional benefit without exacerbation of angina. Each patient studied had advanced coronary heart disease and ischemic cardiomyopathy, and our results may not be applicable to patients with other forms of cardiomyopathy or to those with valvular heart disease.

In conclusion, angiotensin-converting enzyme inhibitors produce systemic vasodilatation and improve cardiac function in patients with CHF due to ischemic disease. Coronary sinus blood flow and myocardial oxygen extraction are not altered despite a decrease in the rate-pressure product. Angiotensin-converting enzyme inhibition exerts no coronary vasomotor effect in advanced ischemic cardiomyopathy, either as a consequence of limited coronary vascular reserve, a lack of angiotensin-mediated coronary vasoconstriction, or the minimal overall change in myocardial metabolic demands during this form of vasodilator therapy. Nevertheless, angiotensin inhibition improves myocardial efficiency in ischemic cardiomyopathy and appears useful in the management of patients with this disorder.

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We thank Carolyn H. McCabe for help with statistical analysis and Ruby Gordon for skilled secretarial assistance.

Appendix: Hemodynamic Equations

$$LVSWI = (AP_s - PW)SVI \times 0.0136$$

$$SVR = [(AP - RA)/CO] \times 80$$

$$CSBF = (T_b - T_i)/(T_b - T_m) - 1\ (1.08 \times 50)$$

$$CVR = (AP - RA)/CSBF \times 80$$

$$MVO_2 = A_{O_2} - CS_{O_2}) \times CSBF$$

$$EME = (LVSWI/MVO_2) \times 100$$

A_{O_2} = arterial oxygen content (vol/100 ml); AP = mean arterial blood pressure (mm Hg); AP_s = systolic arterial blood pressure (mm Hg); CO = cardiac output (liters/min); CSBF = coronary sinus blood flow (ml/min); CS_{O_2} = coronary sinus oxygen content (vol/100 ml); CVR = coronary vascular resistance (dynes·s·cm^{-5}); EME = external myocardial efficiency (%); LVSWI = left ventricular stroke-work index (g·m/m^2); MVO_2 = myocardial oxygen consumption (ml/min); PW = mean pulmonary capillary wedge pressure (mm Hg); RA = mean right atrial pressure (mm Hg); SVI = left ventricular stroke-volume index (ml/beat/m^2); SVR = systemic vascular resistance (dynes·s·cm^{-5}); T_b, T_i, T_m = temperatures of blood, indicator, and blood-indicator mixture, respectively (°C).

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Accuracy of Cardiac Output, Oxygen Uptake, and Arteriovenous Oxygen Difference at Rest, During Exercise, and After Vasodilator Therapy in Patients With Severe, Chronic Heart Failure

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Measurement of cardiac output, arteriovenous oxygen difference, and oxygen uptake in patients with heart failure may be subject to technical and biologic inaccuracies. We measured these 3 variables in 16 patients with chronic heart failure at rest and during exercise. When cardiac output was measured by thermodilution and compared with values calculated by the Fick principle, there was a significant correlation at rest ($r = 0.91$, $p < 0.001$) and at exercise ($r = 0.93$, $p < 0.001$). When the arteriovenous oxygen difference was measured by spectrophotometry of arterial and mixed venous samples and compared with values calculated by the Fick principle, there was a significant correlation at rest ($r = 0.80$, $p < 0.01$) and at exercise ($r = 0.76$, $p < 0.01$). When oxygen uptake was measured from expired gas analysis and compared with values calculated by the Fick principle, there was a significant correlation at rest ($r = 0.84$, $p < 0.01$) and at exercise ($r = 0.94$, $p < 0.001$). In addition, 10 patients received vasodilator treatment which increased cardiac output and decreased the arteriovenous oxygen difference at rest and exercise. There was no significant difference between measured and calculated values for the 3 variables under those additional conditions. It is concluded that despite technical and biologic difficulties, cardiac output, arteriovenous oxygen difference, and oxygen uptake, when calculated from Fick's principle, yield results equivalent to direct measurement.

Renewed interest in the exercise physiology of patients with severe heart failure has been spurred by the relative safety of procedures such as invasive hemodynamics and exercise, and by the desire to evaluate responses to new therapies. Measurement of cardiac transport and gas exchange involves 3 variables—arteriovenous oxygen difference, cardiac output, and oxygen uptake—which are inextricably linked during the steady state. Innumerable recent reports have employed different techniques to measure the 3 variables in Fick's equation. It has not been possible to compare the results of these reports because studies of reproducibility correlating different techniques are not available. Physiologic changes and pharmacologic interventions in patients with heart failure impose technical difficulties or biological uncertainties which may void the assumptions of Fick's principle, on which such measurements are based. We examined the interrelation among these 3 variables and assessed individual patients during exercise and during arteriolar vasodilator treatment to define the accuracy of these data.

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Methods

Patients: Sixteen patients with chronic heart failure, with severe left ventricular dysfunction secondary to idiopathic cardiomyopathy or ischemic heart disease, were studied to assess cardiovascular transport. These patients had been referred to our medical center because of intractable symptoms of heart failure. Some were studied as part of advanced diagnostic testing, while others were part of experimental drug protocols. Where appropriate, these protocols were approved by the Human Subjects Committee of this institution. In-

TABLE I Supine Resting Hemodynamic Variables*

Heart rate (min^{-1})	82 ± 16
Mean arterial pressure (mm Hg)	87 ± 14
Mean pulmonary arterial pressure (mm Hg)	40 ± 8
Pulmonary capillary pressure (mm Hg)	26 ± 6
Right atrial pressure (mm Hg)	14 ± 6
Cardiac index (liters/min·m^2)	2.0 ± 0.5
Left ventricular ejection fraction	0.22 ± 0.07

* Values are mean ± standard deviation for 16 patients.

formed written consent was obtained for all procedures. Thirteen patients were men and 3 were women, and their mean age was 58 years (range 33 to 78). Each patient had severe symptoms of exercise intolerance due to fatigue, dyspnea, or both (New York Heart Association class III).[1] Supine resting hemodynamics and ejection fraction averages (Table I) showed severe abnormalities of left ventricular function in each patient and abnormalities of right ventricular function in some patients.

Measurement and calculation of arteriovenous oxygen difference: The arteriovenous oxygen difference ($AV\text{-}O_2$; ml/dl; standard temperature and pressure, dry [STPD]) was measured as the difference between the oxygen content of arterial and mixed venous blood (Ca-Cv) and for comparison was calculated as the quotient of oxygen uptake divided by cardiac output ($\dot{V}O_2/CO$) (for details of these methods, see later). Aliquots of arterial and mixed venous blood were simultaneously analyzed in a gas tension/pH analyzer (model 175, Corning Instruments, Medfield, Massachusetts) and in a quadruple beam spectrophotometer (IL 282, Instrumentation Laboratory, Cambridge, Massachusetts). The accuracy of the blood gas analyzer is ±1.0 torr for oxygen and carbon dioxide tensions and ±0.01 for pH. The accuracy of the spectrophotometer is ±0.01 for absolute oxygen saturation fraction and ±0.3 g/dl for hemoglobin. Oxygen saturation was measured directly by the spectrophotometer at 37°C.[2] Oxygen contents (Ca and Cv) were calculated as follows: $(Hgb \times S \times 1.34) + (PO_2 \times 0.003)$, where Hgb is the hemoglobin concentration (g/dl), 1.34 is the empirical value of oxygen capacity of a gram of hemoglobin, S is the oxygen saturation expressed as a fraction (determined by the spectrophotometer), and PO_2 is the oxygen tension (determined by the blood gas analyzer). The first component in the equation represents the blood oxygen carried by hemoglobin; the second component represents the blood oxygen dissolved in solution.

Measurement and calculation of cardiac output: Cardiac output (CO, liters/min) was measured by right heart thermodilution and for comparison was calculated as the quotient of oxygen consumption divided by the arteriovenous oxygen difference ($\dot{V}O_2/AV\text{-}O_2$) (for details of $\dot{V}O_2$, see later). For thermodilution, 10 ml of iced 5% dextrose in water solution was rapidly injected into the right atrial part of the Swan-Ganz catheter while the temperature transient was detected by the thermistor in the pulmonary artery.[3] Calculation of cardiac output was performed on-line by a cardiac output computer (model 9520A, Edwards Laboratories, Santa Ana, California). The variation among quadruple cardiac outputs obtained while the patients were at rest was less than 10%.

Measurement and calculation of oxygen uptake: Oxygen uptake ($\dot{V}O_2$; ml/min; STPD) was measured by the open-circuit technique (collection of expired gas) and for comparison was calculated as the product of cardiac output and arteriovenous oxygen difference ($CO \times AV\text{-}O_2$). For the open-circuit technique, patients breathed room air through a mouthpiece connected to a low resistance two-way valve (modified Otis-McKerrow, Collins, Cambridge, Massachusetts), and expired gas was directed through a short length of tubing, and then through a low resistance three-way valve (model 7210, Collins) into a latex meteorologic balloon (model 80 MRL, Kaysam, Piscataway, New Jersey). The expired gas in the balloons was measured for fractional oxygen (F_EO_2) and carbon dioxide (F_ECO_2) concentrations by a medical mass spectrometer (model MGA 1100, Perkin Elmer, Pomona, California) calibrated with gravimetrically analyzed gases. Expired minute ventilation ($\dot{V}_E$) was determined by timing the gas collection and measuring the collected volume in a water-seal gasometer (120 liter gasometer, Collins). Volumes in the gasometer were corrected from ambient temperature and pressure, saturated [ATPS] to STPD. Oxygen uptake was calculated as follows: $\dot{V}O_2 = \dot{V}_E [0.265 \times (1.00 - F_EO_2 - F_ECO_2) - F_EO_2]$. This equation corrects for the difference between inspired and expired gas volumes by assuming that inert gas volumes are constant. The accuracy of the mass spectrometer is ±0.1% for oxygen absolute and ±0.01% for carbon dioxide absolute. The accuracy of the gasometer is ±70 ml.

Exercise protocol: Patients performed incremental exercise on a weight-flywheel cycle ergometer.[4] Stages were 3 minutes in duration beginning with unloaded pedalling—that is, only work required to turn the unloaded flywheel—and increased by 160 kpm/min (25 W) per stage. Patients exercised to their symptom-limited maximum as determined by the patients themselves as the point of intolerable dyspnea, generalized fatigue, or both, or leg fatigue. The final stage of exercise was frequently prolonged to 4 to 6 minutes to allow completion of measurements. In the patients reported here, peak work load ranged from unloaded pedalling (0 load) in severely disabled patient up to 480 kpm/min (75 W).

Drug protocol: An arteriolar vasodilator was administered orally in incremental doses so as to increase cardiac output at least 20% over control values at rest and exercise. Hydralazine was administered every 6 hours with a range of peak doses from 50 to 150 mg every 6 hours. Minoxidil was administered every 12 hours with a range of peak doses from 5 to 20 mg every 12 hours. Doses were administered over a range of 36 to 72 hours before the patients were retested. Patients were restudied 2 hours after a drug dose. All patients were also taking digoxin and furosemide, and these were continued throughout the study.

Measurement protocol: Measurements were made at 2 conditions (rest and peak exercise) and at 2 treatments (control and drug). Sixteen patients had measurements at rest and peak exercise during control treatment. Ten of these patients also had measurements at rest and peak exercise during drug treatment. We made measurements at rest after the patients had been sitting on the bicycle for 10 minutes, and used the following protocol. After the first thermodilution cardiac output determination was completed, a 3 minute gas collection was begun simultaneously with a second thermodilution cardiac output determination. At the end of the second cardiac output determination, arterial and duplicate mixed venous blood samples were obtained for oxygen content. This blood sampling took approximately 1 minute during the middle of the gas collection. The end of the third thermodilution cardiac output determination approximately coincided with the end of the gas collection, and then a fourth cardiac output determination was performed. The sampling regimen was slightly modified during exercise so as to decrease the period of the measurements during exercise. A 60 to 90 second gas collection was performed beginning with the second thermodilution cardiac output determination, and gas

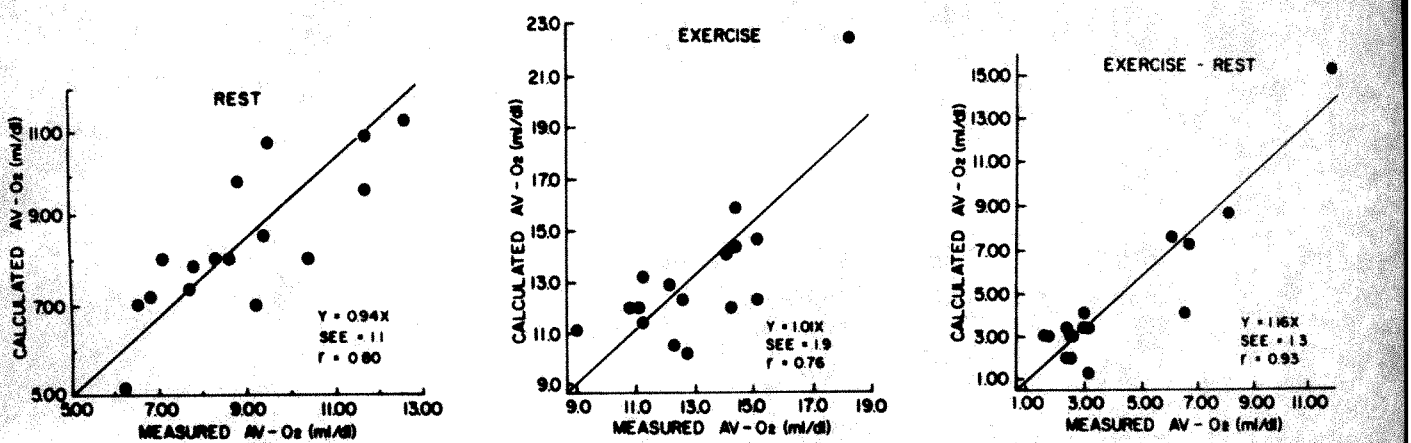

FIGURE 1. Measured compared with calculated arteriovenous oxygen difference ($AV\text{-}O_2$). Appearing in each panel is the regression line (constrained to pass through the zero-zero intercept), the regression equation, the standard error of the estimate (SEE), and the correlation coefficient (r). Each correlation was very significant ($p < 0.01$). Each regression line slope coefficient was not different from a slope of 1.0. **Left panel,** comparison at rest. **Center panel,** comparison during exercise. **Right panel,** comparison of differences between rest and exercise. An exception was found in the statistical testing of slope (see text).

collection continued with the blood sampling. A third cardiac output determination was performed coincident with the end of gas sampling.

Data analysis: No datum was discarded in any patient. The investigators were satisfied that all measurements were obtained accurately. The measured variables of arteriovenous oxygen difference, cardiac output, and oxygen uptake were compared with the calculated variables by regression analysis[5] at rest, during exercise, and for changes between rest and exercise. There was no a priori reason to believe that the calculated variables were systematically different from the measured variables. Therefore, the regression lines were constrained to pass through a zero intercept. The deviation of the slope of the regression line from 1.0 measures the extent to which the measured and calculated variables disagree. In addition, the slope of the line was tested to determine whether or not it was statistically different from a slope of 1.00. The zero order correlation coefficient was obtained for all regressions and measures the linear dependence between measured and calculated variables. The standard error of the estimate provides a measure of the fit of the data to the regression line.

We also recognized another question appropriate for statistical testing: Is there equality of the data sets for measured and calculated data under both control and vasodilator therapy? Analysis of variance was used to compare the measured and calculated data under the control and vasodilator conditions. The statistical model utilized was a 3 factor analysis of variance with repeated measures on all factors.[6] The 2 levels of the first factor were the measured and calculated conditions, the 2 levels of the second factor were the presence and absence of vasodilator therapy, and the 2 levels of the third factor were the rest and exercise conditions. The levels of significance presented in the current study represent probabilities derived from a test of the main effect for the measured and calculated factor. Statistical significance was set at the 0.05 level ($p \leq 0.05$).

Results

The terms *measured* and *calculated*, as used herein, refer to our definitions as provided in the Methods section.

Arteriovenous oxygen difference (Fig. 1, Table II): The range of arteriovenous oxygen content difference during control therapy was from 6.2 to 18.4 ml/dl. Modest and significant ($p < 0.01$) correlation coefficients were found between measured and calculated values at rest ($r = 0.80$) and during exercise ($r = 0.76$) and for the change between rest and exercise ($r = 0.93$). The slope of the regression line was not different from a slope of 1.0 for rest and exercise conditions, but was different for the change between rest and exercise. For the 10 patients whose data were examined under 4 conditions, (control rest, control exercise, vasodilator rest, and va-

TABLE II Measured and Calculated Variables for Patients Treated With Vasodilators

	Measured				Calculated				
	CR	CE	VR	VE	CR	CE	VR	VE	p
$AV\text{-}O_2$ (ml/dl) (n = 10)	8.6 ± 1.8	13.8 ± 2.1	5.8 ± 1.1	11.6 ± 2.6	7.9 ± 1.6	13.5 ± 3.6	5.7 ± 0.9	11.7 ± 3.2	NS (>0.20)
CO (liters/min) (n = 10)	3.6 ± 1.1	4.9 ± 1.5	4.7 ± 0.7	5.9 ± 1.4	3.4 ± 1.1	4.8 ± 1.7	4.7 ± 0.9	6.0 ± 1.7	NS (>0.20)
VO_2 (ml/min) (n = 10)	273 ± 63	658 ± 249	267 ± 39	699 ± 255	296 ± 57	667 ± 217	269 ± 37	695 ± 250	NS (>0.20)

Values are mean ± standard deviation. $AV\text{-}O_2$ = arteriovenous oxygen difference; CE = control treatment during exercise; CO = cardiac output; CR = control treatment at rest; n = number of patients; NS = not significant; p = significance of difference between measured and calculated values. VE = vasodilator treatment during exercise; VO_2 = oxygen uptake; VR = vasodilator treatment at rest.

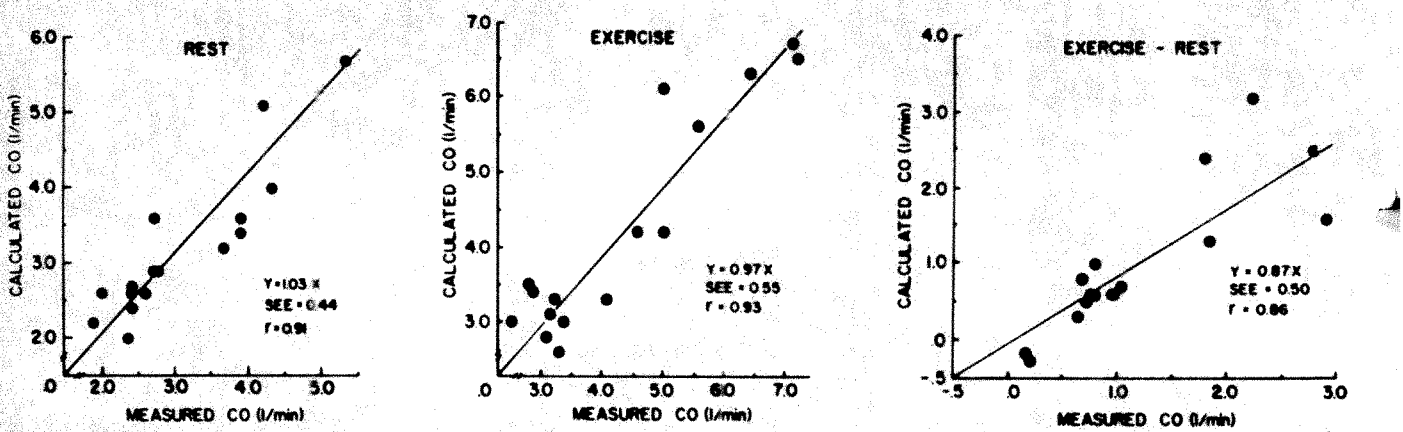

FIGURE 2. Measured compared with calculated cardiac output (CO). Data were analyzed by linear regression. Symbols, panel arrangement, and results of statistical testing are similar to those in Figure 1.

sodilator exercise), there was no significant difference between measured and calculated arteriovenous oxygen difference across the conditions.

Cardiac output (Fig. 2, Table II): The range of cardiac output during control therapy was 2.0 to 6.7 liters/min. High and significant ($p < 0.01$) correlation coefficients were found between measured and calculated values at rest ($r = 0.91$) and during exercise ($r = 0.93$) and for the change between rest and exercise ($r = 0.86$). The slopes of the regression lines under these conditions were not different from 1.0. For the 10 patients whose data were examined under 4 conditions (control rest, control exercise, vasodilator rest, and vasodilator exercise), there was no significant difference between measured and calculated cardiac output across the conditions.

Oxygen uptake (Fig. 3, Table II): The range of oxygen uptake during control therapy was 165 to 1,028 ml/min. High and significant ($p < 0.01$) correlation coefficients were found between measured and calculated values at rest ($r = 0.84$) and during exercise ($r = 0.94$) and for the change between rest and exercise ($r = 0.95$). The slopes of the regression lines under these conditions were not different from 1.0. For the 10 patients whose data were examined under 4 conditions (control rest, control exercise, vasodilator rest, and vasodilator exercise), there was no significant difference between measured and calculated oxygen uptake across the conditions.

Discussion

There is no single comprehensive report on the comparison of methods of measurement of cardiac output and gas exchange variables in patients with heart failure. Our report is unique because of the heart failure patient population, the rest and exercise conditions of the study, and the drug interventions used—all of which are expected to change the actual measured quantities and the time to steady-state values.

Comparison of methods of measurement: We measured the oxygen content of arterial and mixed venous blood by spectrophotometry, we measured cardiac output by thermodilution, and we measured oxygen uptake by analysis of expired gas. As a comparison, we applied Fick's principle as another method of measuring these 3 variables. The comparison between methods was performed in patients with severe chronic heart failure at rest, during maximum cycle ergometry, and again

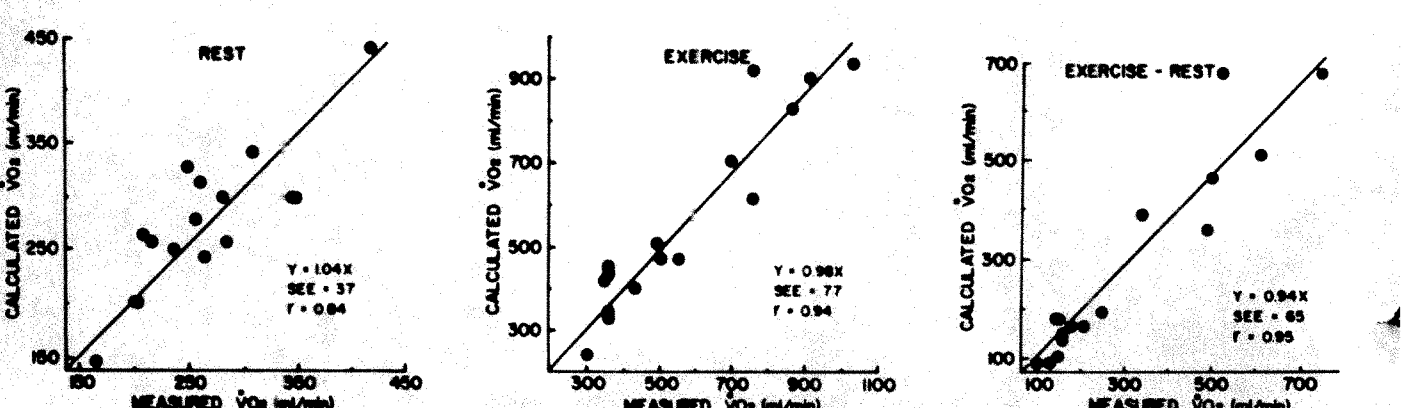

FIGURE 3. Measured compared with calculated oxygen consumption ($\dot{V}O_2$). Data were analyzed by linear regression. Symbols and panel arrangement as in Figure 1.

after drug intervention had increased cardiac output (and decreased the arteriovenous oxygen difference). We found high and very significant linear correlations between the methods at rest and during exercise and the change between rest and exercise. We compared the 2 methods of measurement of these 3 variables under 4 conditions (control treatment at rest, control treatment during exercise, vasodilator treatment at rest, and vasodilator treatment during exercise) by analysis of variance. We found no difference between the methods. We conclude that there is no large or systematic difference between these 2 methods of measurement.

Cardiac output: We measured cardiac output by thermodilution and compared it with calculated cardiac output (oxygen uptake/arteriovenous oxygen difference). We demonstrated high correlations during various conditions. In addition to biologic considerations, there are a myriad of technical considerations in the measurement of blood flow by indicator dilution technique. Special concern might be expressed about patients with chronic heart failure. Very low cardiac output might lead to a loss of cold indicator, to poor mixing, to nonmonoexponential washout of indicator, or to reappearance before washout is complete. These problems may be compounded in the use of right-heart thermodilution in the presence of tricuspid regurgitation. In fact, 6 of our patients did have clinically obvious tricuspid regurgitation secondary to right ventricular failure. Nevertheless, the linear correlations between measured and calculated variables were high and very significant. The linear regression slope was not different from 1.0, and there was no systematic offset (intercept not different from 0.0). Even higher correlations than ours have been reported[7] when thermodilution was compared with dye dilution in low cardiac output states. Despite multiple studies comparing thermodilution with other techniques for measuring cardiac output at rest, we were able to find only 1 report with scanty data at exercise; similar high correlations were reported.[8]

Oxygen uptake: We measured oxygen uptake by analysis of expired gas and compared it with calculated oxygen uptake (cardiac output × arteriovenous oxygen content difference). We demonstrated high correlations during various conditions. In comparing these 2 methods, one should take into account 2 biologic considerations. One consideration is that oxygen uptake is in the steady state. It may not be possible to obtain steady-state conditions of oxygen uptake using short work load durations near maximal oxygen uptake, as is the customary protocol for many studies including this one.[9] Nevertheless, the time constant of oxygen intake is short and, more importantly, at low levels of oxygen uptake the increments observed during non-steady state are very small.[10] Another consideration is the equality of oxygen uptake to tissue oxygen utilization, which implies no change in available oxygen stores (lung air, blood hemoglobin, or muscle myoglobin). The equality between uptake and tissue utilization is probably not correct, but the difference is believed small. These considerations could affect our 2 methods to slightly different degrees. There are also many technical considerations of oxygen uptake measurement that could affect both of our methods of measurement. Nevertheless, we found the linear correlation coefficients between measured and calculated values were high and very significant. The linear regression slope was not different from 1.0 and there was no systematic offset (intercept not different from 0.0).

Arteriovenous oxygen content: We measured the arteriovenous oxygen content difference by spectrophotometry and compared it with the calculated content difference (oxygen uptake/cardiac output). The 2 most important technical considerations of the spectrophotometric method of measuring oxygen saturation are related to a predictable relation between light absorbance and oxygen saturation, and the detection of all hemoglobin species. With measurement by spectrophotometry in *whole blood*, there is a linear relation between oxygen saturation and absorbance only down to 0.40 saturation, which limits the range of frequently used equipment (such as standard dual wave length oximeters as found in many catheterization laboratories). This limitation is not present with *hemoglobin in solution*, and modern spectrophotometers such as the one used in this study employ agents which lyse erythrocytes. Another technical consideration of oximetry is the measurement of all hemoglobin species, since oxygen saturation really represents the fraction of oxygenated hemoglobin compared with all hemoglobin species. The equipment used in this study detects all 4 common hemoglobin species. Under very rare circumstances, however, small amounts of some other hemoglobin species could be present or the hemoglobin molecule could be aberrant.

We only found modest (but significant) linear correlations between measured and calculated arteriovenous oxygen differences. However, the slope of the regression line was not different from1.0 at rest and during exercise, and there was no systematic offset (intercept of line not different from 0.0). There are 2 possible explanations for the lower correlations. First, we infer that measured arteriovenous oxygen difference has little technical variability while calculated arteriovenous oxygen difference has more variability. Similar results can be inferred from a recent report[11] which applied these comparable methods during dog studies. Calculated arteriovenous oxygen difference is the quotient of oxygen uptake divided by cardiac output, each having some variability when separate and greater variability when they appear in the same equation. In contrast, when measured arteriovenous oxygen difference is included as part of the quotient of a calculated variable (such as $\dot{V}O_2/AV\text{-}O_2$) or as part of the product of a calculated variable (such as $CO \times AV\text{-}O_2$), overall variability is reduced and the correlation coefficient is increased. This implies that for the highest accuracy, the arteriovenous oxygen difference should be measured rather than calculated. Second, however, our samples for arteriovenous oxygen difference were drawn only in the middle of a much longer sampling period of cardiac output and oxygen uptake. Therefore, if conditions were not steady state, the lower correlations we observed

might be due to a less-than-optimal sampling protocol.[12]

In summary, manipulation of Fick's equation provides the opportunity to directly measure or indirectly calculate arteriovenous oxygen difference, cardiac output, or oxygen uptake. The limitations and technical demands of each technique must be appreciated. Extremely ill patients with severe left ventricular dysfunction present an exceptional challenge to mensuration under varying conditions and during repeated measurements. For the most part, there appears to be good correlation between measured and calculated techniques.

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Effects of Amyl Nitrite on Left Ventricular Relaxation In Patients With Borderline Hypertension

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The effects of systemic hypertension on left ventricular relaxation properties remain largely undefined. To assess such effects 22 normal volunteers and 15 patients with borderline hypertension were examined. The tangent to the echocardiographic left ventricular posterior wall endocardium was measured in diastole and was normalized for end-diastolic dimension to yield normalized velocity of relaxation. This velocity of relaxation was measured at rest and throughout inhalation of amyl nitrite. Mean value ± standard deviation (SD) from rest to peak amyl nitrite effect for the normal group and for the patients with borderline hypertension was 3.3 ± 0.6 → 7.2 ± 1.1 and 3.0 ± 0.8 → 4.4 ± 1.1 s^{-1}, respectively. All 22 persons in the normal group and 2 of the 15 patients with borderline hypertension attained normalized velocity of relaxation greater than 5.5 s^{-1} with administration of amyl nitrite. Multivariate analysis in the normal group identified heart rate, mean arterial pressure, and fractional shortening as the best predictors of normalized left ventricular relaxation velocity ($r = 0.85$; $p < 0.001$). The increase in the normalized velocity of relaxation induced by amyl nitrite is blunted in patients with borderline hypertension. These changes in left ventricular relaxation identify early cardiac involvement and may prove clinically useful in hypertensive patients.

Sustained systemic hypertension causes changes in cardiac structure and function which, when severe enough, can be recognized on routine electrocardiography and chest roentgenography,[1] but these changes occur relatively late in the course of hypertension. Echocardiography can accurately assess cardiac alterations induced by hypertension and identify the various degrees of left ventricular hypertrophy[2] and abnormal systolic performance.[1,3] Furthermore, echocardiography has demonstrated impairment in left ventricular function in hypertensive patients with minor electrocardiographic abnormalities.[4] Recently, a high incidence of echocardiographic abnormalities was detected in asymptomatic hypertensive patients in the absence of electrocardiographic or radiographic abnormalities.[5]

Because borderline hypertension predisposes to increased morbidity and mortality from cardiovascular disease,[6,7] a simple noninvasive method of identifying early cardiac involvement might have important clinical applications. Patients with borderline hypertension and early cardiac damage may require more careful follow-up and early institution of antihypertensive measures.

Echocardiographic studies describing left ventricular relaxation variables rather than systolic function in health and disease states are scarce.[8–10] This study was designed to assess the effects of borderline hypertension on one of these variables, the left ventricular velocity of relaxation.

Methods

The control group was composed of 22 normal subjects (17 women and 5 men; mean age ± SD, 26.2 ± 7.2 years) without clinical evidence of heart disease. Echocardiography was performed at rest and during inhalation of amyl nitrite, a drug chosen because of its substantial effects on heart rate, blood pressure, and left ventricular volume.[11] In 6 of these subjects, the amyl nitrite test was repeated after a 25 minute interval of rest.

Fifteen patients (5 women and 10 men; mean age 33.3 ± 10.1 years) were referred for evaluation of borderline hypertension, defined as blood pressure readings greater than 140/90 mm Hg on at least 3 outpatient visits but normal pressure recorded

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TABLE I Hemodynamic and Echocardiographic Effects of 2 Separate Amyl Nitrite Challenges in 6 Normal Subjects

		1st AN Test (n = 6)	2nd AN test (n = 6)
HR (beats/min)	Rest	65.0 ± 3.8	63.3 ± 3.1
	AN	115.0 ± 10.8*	114.8 ± 6.7*
MAP (mm Hg)	Rest	85.2 ± 9.9	80.8 ± 10.1
	AN	59.0 ± 15.2†	56.8 ± 9.0‡
MAP × R-R (mm Hg × s)	Rest	79.4 ± 11.6	76.8 ± 11.3
	AN	30.7 ± 7.2*	29.8 ± 4.5*
Dd (mm)	Rest	47.7 ± 4.8	47.3 ± 3.9
	AN	44.3 ± 4.4†	43.7 ± 4.9‡
Ds (mm)	Rest	32.7 ± 3.1	30.8 ± 2.0
	AN	24.2 ± 3.4*	24.2 ± 3.8‡
$\overline{Vcf}$ (circ/s)	Rest	1.06 ± 0.09	1.20 ± 0.20
	AN	1.77 ± 0.20*	1.73 ± 0.26‡
FS (%)	Rest	31.4 ± 2.2	34.7 ± 4.6
	AN	45.6 ± 3.5*	44.8 ± 3.8†
NVR (s^{-1})	Rest	3.3 ± 0.5	3.3 ± 0.5
	AN	7.3 ± 1.1*	7.7 ± 1.3*

Values are given as mean ± standard deviation.
* $p < 0.001$ compared with resting value; † $p < 0.05$; ‡ $p < 0.005$.
AN = amyl nitrite; circ = circumference; Dd = left ventricular end-diastolic dimension; Ds = left ventricular end-systolic dimension; FS = fractional shortening; HR = heart rate; MAP = mean arterial pressure; NVR = normalized velocity of relaxation of the posterior left ventricular wall; R-R = cycle length; Vcf = mean velocity of circumferential fiber shortening.

TABLE II Peak Effect of Amyl Nitrite on Echocardiographic and Hemodynamic Variables in Normal Subjects and Patients With Borderline Hypertension

		Normal Subjects (n = 22)	Hypertensive Patients (n = 15)
HR (beats/min)	Rest	66.5 ± 9.4	71.2 ± 14.7
	AN	113.8 ± 12.6*	107.2 ± 13.5*
MAP (mm Hg)	Rest	84.3 ± 9.1	105.5 ± 10.7
	AN	60.0 ± 11.1*	79.4 ± 16.5*
MAP × R-R (mm Hg × s)	Rest	77.3 ± 11.1	92.7 ± 22.0
	AN	32.1 ± 7.5*	44.4 ± 8.0*
Dd (mm)	Rest	46.1 ± 4.1	50.6 ± 4.9
	AN	43.1 ± 4.0*	46.9 ± 5.6*
Ds (mm)	Rest	29.5 ± 4.4	30.1 ± 5.5
	AN	22.4 ± 4.2*	24.3 ± 5.6*
$\overline{Vcf}$ (circ/s)	Rest	1.22 ± 0.21	1.43 ± 0.34
	AN	1.89 ± 0.43*	2.01 ± 0.41
FS (%)	Rest	36.3 ± 6.3	40.5 ± 8.6
	AN	48.2 ± 7.2*	48.5 ± 8.5*
NVR (s^{-1})	Rest	3.3 ± 0.6	3.0 ± 0.8
	AN	7.2 ± 1.1*	4.4 ± 1.1*

Values are given as mean ± standard deviation.
* $p < 0.001$ compared to resting value.
Abbreviations as in Table I.

at other times.[6,7] All were asymptomatic and showed no evidence of target organ damage. All patients had regular sinus rhythm with electrocardiographic findings that were considered normal, and they did not fulfill any criteria for left ventricular hypertrophy or left atrial conduction abnormalities. At the time of the study no patient was receiving any therapy. All patients and normal subjects gave informed consent.

Echocardiograms were recorded using a Unirad model C echocardiograph and a 2.25 MHz transducer. High quality echograms of the left ventricular cavity, just below the posterior leaflet of the mitral valve, were recorded on a Honeywell Visicorder, model 1856, along with simultaneous electrocardiograms. Blood pressures were taken by standard sphygmomanometric methods and were expressed as mean arterial pressure estimated as the sum of the diastolic pressure plus one third of the pulse pressure. External carotid pulse tracings, phonocardiograms, and blood pressure were recorded simultaneously with the echocardiogram at rest and at intervals of 15, 30, 45, 60, and 120 seconds from beginning of inhalation of amyl nitrite. The left ventricular ejection time was measured from the external carotid pulse recording.

Recordings of the posterior wall endocardium were analyzed as described by Fogelman et al.[9] and Wise.[10] The velocity of left ventricular relaxation was determined by drawing a tangent to the steepest point of the diastolic limb of the posterior wall endocardium. At least 3 beats from each recording were analyzed, and the average value was reported. The ventricular end-diastolic dimension was measured at the height of the electrocardiographic R wave,[12] and the left ventricular end-systolic dimension was measured at the summit of the posterior wall endocardium.[12] The concept of normalized velocity, as described by Mirsky et al.,[13] has previously been employed in the echocardiographic evaluation of left ventricular function.[14] The same concept is used in the present study to evaluate left ventricular relaxation to permit meaningful comparison among patients.

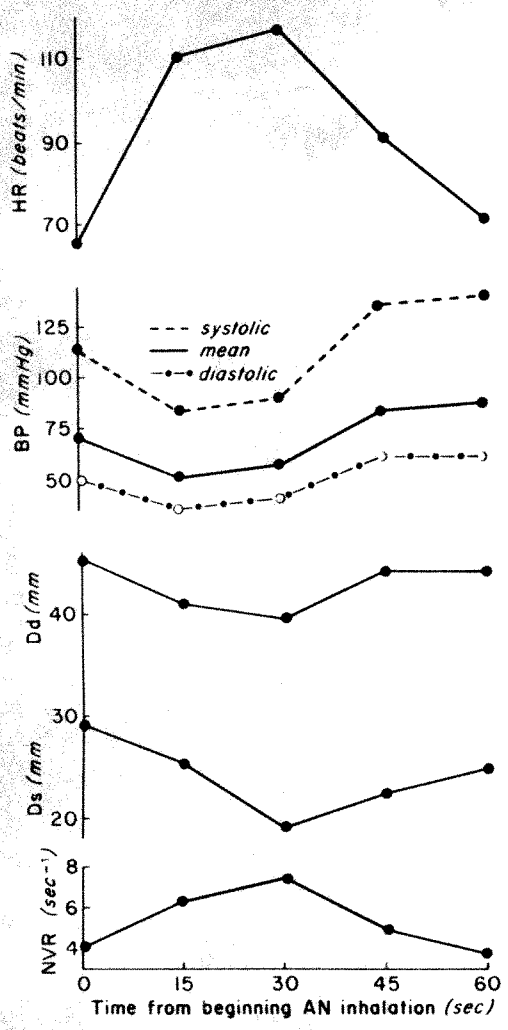

FIGURE 1. Typical effects of amyl nitrite inhalation in a normal subject. AN = amyl nitrite; BP = blood pressure; Dd = left ventricular end-diastolic dimension; Ds = left ventricular end-systolic dimension; HR = heart rate; NVR = normalized left ventricular relaxation velocity; sec = seconds.

Normalized velocity of left ventricular relaxation (NVR) was calculated according to the formula NVR (s^{-1}) = VR/Dd, where VR = left ventricular relaxation velocity in centimeters per second and Dd = left ventricular end-diastolic dimension in centimeters. The mean rate of circumferential fiber shortening ($V\bar{c}f$) was calculated according to the formula ($V\bar{c}f$ (circ/s) = (Dd − Ds)/(Dd × LVET), where circ = circumference, Dd = left ventricular end-diastolic dimension in centimeters, Ds = left ventricular end-systolic dimension in centimeters, and LVET = left ventricular ejection time. The fractional shortening (FS) of the left ventricular internal dimension was calculated according to the formula FS = (Dd − Ds)/Dd, where Dd = left ventricular end-diastolic dimension in centimeters and Ds = left ventricular end-systolic dimension in centimeters.

Quantitative assessment of the hemodynamic effect of amyl nitrite was estimated from the change in the product of the mean arterial pressure multiplied by the cycle length and the product expressed in mm Hg × seconds. Normalized velocity of relaxation was assigned as a dependent variable whereas age, heart rate, mean arterial pressure, fractional shortening, left ventricular end-diastolic dimension, and left ventricular end-systolic dimension were considered predictor variables. Data were analyzed using a multivariate statistical analysis. The multivariate linear model routine of the Statistical Package for Social Sciences[15,16] is used to test the hypothesis of no correlation between normalized velocity of relaxation and the predictor variables. The hypothesis of equality of group means was evaluated using the unpaired or paired t test as appropriate between the normal and the borderline hypertensive groups.[15]

Results

At the time of the study the mean ± SD resting systolic and diastolic pressures were 109.3 ± 10.7 and 71.9 ± 9.7 mm Hg for the normotensive subjects and 140.5 ± 14.8 and 90.3 ± 12.0 mm Hg for the borderline hypertensive patients, respectively. No significant difference was noted in the following echocardiographic variables between the normotensive and borderline hypertensive groups: left ventricular end-diastolic and end-systolic dimensions, interventricular septal thickness, posterior wall thickness, and left atrial size. The normal responses of heart rate, blood pressure, left ventricular end-diastolic and end-systolic dimensions, and normalized left ventricular relaxation velocity to amyl nitrite are shown in Figure 1. In the 6 normal subjects undergoing 2 separate amyl nitrite challenges 25 minutes apart, mean resting normalized left ventricular velocity of relaxation during the 2 control periods were identical at 3.3 ± 0.5 s^{-1}. The consistency and reproducibility of the hemodynamic effects of amyl nitrite are shown in Table I, which compares the changes in the variables measured before and at peak effect of amyl nitrite during 2 separate challenges in these first 6 normal subjects. The results showed that amyl nitrite produced nearly the same hemodynamic changes in the same person.

The values for the normalized left ventricular velocity of relaxation for the 22 normal subjects at rest and at peak effect of amyl nitrite were 3.3 ± 0.6 and 7.2 ± 1.1 s^{-1}, respectively ($p < 0.001$). Heart rate, fractional shortening, and circumferential fiber shortening increased significantly while left ventricular end-diastolic and end-systolic dimensions as well as mean arterial pressure decreased at peak effect of amyl nitrite (Table II). In every instance, amyl nitrite induced a marked increase in the normalized left ventricular relaxation velocity. In no instance did this value fail to reach 5.5 s^{-1} or more at peak amyl nitrite effect.

In the 22 normal subjects we were able to collect echocardiographic and electrocardiographic data and blood pressure and external carotid recordings at different intervals from the beginning of inhalation of amyl nitrite until the peak effect of the drug was reached. These recordings yielded 77 data points in the 22 subjects. Heart rate, mean arterial pressure, left ventricular end-systolic dimension, and fractional shortening showed decreasing influence on the normalized left ventricular relaxation velocity ($r = 0.80, -0.66, -0.59$, and 0.56, respectively). Multivariate linear regressions between normalized left ventricular relaxation

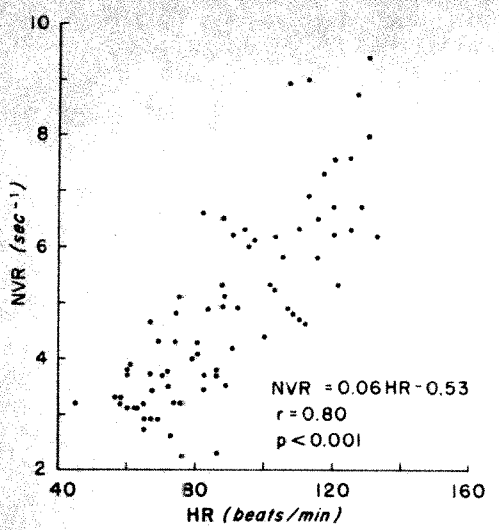

FIGURE 2. Relation between heart rate (HR) and normalized left ventricular relaxation velocity (NVR) during amyl nitrite inhalation in 22 normal subjects. Data points were collected at 15 second intervals from the beginning inhalation of amyl nitrite until the peak effect of the drug was reached.

velocity and predictor variable heart rate, mean arterial pressure, fractional shortening, and left ventricular end-systolic dimension showed a significant correlation coefficient ($r = 0.85$; $p < 0.001$): NVR = 2.72 + 0.05 HR − 0.03 MAP + 1.70 FS −0.02 Ds, where NVR = normalized left ventricular relaxation velocity, HR = heart rate, MAP = mean arterial pressure, and FS = fractional shortening.

The partial regression coefficients for heart rate and mean arterial pressure were statistically significant ($p < 0.001$). Neither fractional shortening nor left ventricular end-systolic dimension contributed significantly to the overall correlation. However, when mean arterial pressure is excluded from the correlation, fractional shortening assumed a significant influence on the normalized left ventricular relaxation velocity. Figure 2 depicts the relation between normalized left ventricular relaxation velocity and heart rate. The interplay between normalized left ventricular relaxation velocity, heart rate, mean arterial pressure, and fractional shortening of the 77 data points from the normal subjects is illustrated by a 3-dimensional graph (Fig. 3).

For the borderline hypertensive patients, the mean resting normalized left ventricular relaxation velocity did not differ significantly from the values in the normotensive group (3.0 ± 0.8 versus 3.3 ± 0.6 s^{-1}, respectively; $p > 0.20$). However, at peak amyl nitrite effect, even though normalized left ventricular relaxation velocity showed similar directional changes in both groups, the control group achieved a significantly higher peak than the patients with borderline hypertension (7.2 ± 1.1 versus 4.4 ± 1.1 s^{-1}; $p < 0.001$), as shown in Figure 4. The increment change of mean arterial pressure-cycle length product showed a comparable decrease in both groups (45.2 ± 11.0 versus 48.3 ± 18.8 mm Hg × s for the normal and the borderline hypertensive groups, respectively; $p = 0.53$).

Within the linear model for normalized left ventricular relaxation velocity, age as the only predictive variable showed a poor correlation ($r = 0.007$). Furthermore, when other predictor variables (heart rate, mean arterial pressure, and fractional shortening) were included, the contribution of age to the overall correlation was insignificant ($F < 1.0$; $p > 0.5$).

For the 2 groups studied, the presence of borderline pressure elevation was compared as an additional variable in the linear model for normalized left ventricular relaxation velocity. This allowed us to evaluate the effect of borderline hypertension on the relaxation velocity after correcting for other predictive variables such as age, heart rate, mean arterial pressure, and fractional shortening. The presence of borderline hypertension correlated with a blunted increase in the normalized left ventricular relaxation velocity in response to amyl nitrite ($p < 0.001$; $F_{1,70} = 31.6$).

Discussion

This study demonstrates that the posterior wall of the left ventricle moves rapidly during diastolic relaxation in normal subjects and those with borderline hypertension. Our values for the normal resting posterior wall endocardial velocity of relaxation are comparable with those previously reported.[9,10] Mean values for the normalized left ventricular posterior wall relaxation velocity did not differ significantly from beat to beat, nor did they change in time when we compared resting values for the 6 normal subjects during 2 control periods. The 2 separate challenges of amyl nitrite in each of the 6 normal subjects showed that amyl nitrite consistently induced nearly the same hemodynamic changes in the same person. The reproducibility of this measured variable of relaxation velocity was established both at rest and after inhalation of amyl nitrite.

Variables predictive of normalized left ventricular relaxation velocity in normal subjects: Relaxation is an active process, requiring approximately 15% of the total myocardial energy probably for pumping calcium back into the sarcoplasmic reticulum.[17,18] Various mechanical and chemical stimuli have been shown to alter left ventricular relaxation.[19–21] Amyl nitrite was chosen as a simple, safe noninvasive challenge to induce changes in factors known to affect the relaxation of the intact left ventricle, such as heart rate, inotropic state, and end-systolic volume.[20,21] All 3 factors were altered by amyl nitrite in each of the subjects studied. In the present study, amyl nitrite consistently increased diastolic velocity of relaxation in every subject. In the normotensive subjects, heart rate, mean arterial pressure, left ventricular end-systolic dimension, and fractional shortening showed decreasing relative influence on normalized left ventricular relaxation velocity. However, the profound effect of heart rate may well be a combination of a direct influence and an indirect one through inotropic stimulation.[21] Although the changes induced by amyl nitrite are those expected from de-

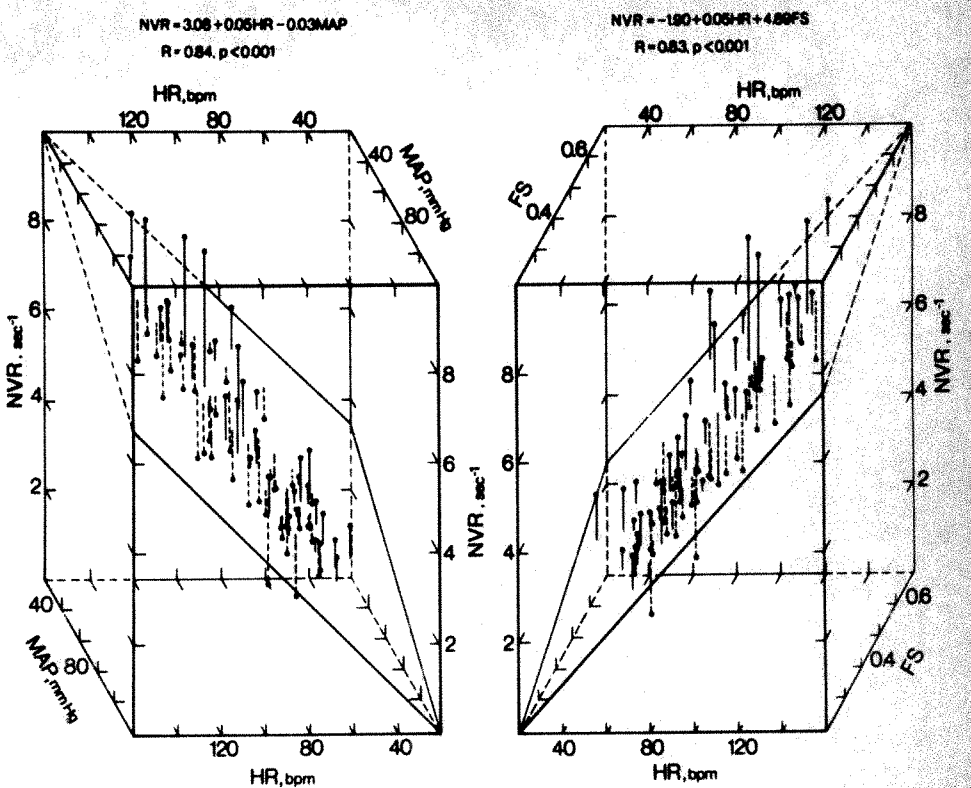

FIGURE 3. Relation between the normalized left ventricular relaxation velocity and its best predictor variables in normal subjects. The cube on the **left-hand side** is a 3-dimensional graph depicting the normalized left ventricular relaxation velocity on the y axis versus mean arterial pressure on the z axis, and heart rate on the x axis. The cube on the **right-hand side** depicts the relation between normalized left ventricular relaxation velocity on the y axis versus heart rate on the x axis and fractional shortening of the z axis. The 2-dimensional plane within each cube is a best fit plane predicted by the equations derived from the multivariate linear model. Data points falling above the planes are connected to them by **solid lines;** points falling below the planes are connected to the planes by **broken lines.** The normalized left ventricular relaxation velocity (NVR) is linearly related to the heart rate (HR) and fractional shortening (FS) and inversely related to mean arterial pressure (MAP).

creased afterload or increased stroke volume,[22] the increase in cardiac output has been shown to be related primarily to the increase in heart rate.[23]

Effects of amyl nitrite on normotensive versus borderline hypertensive subjects: The resting normalized left ventricular relaxation velocity did not discriminate between normal subjects and borderline hypertensive patients, but a striking difference in normalized left ventricular relaxation velocity was seen at peak amyl nitrite effect. None of the 22 normal subjects showed a velocity of less than 5.5 s^{-1}, whereas 13 of 15 patients with borderline hypertension had a velocity of less than 5.5 s^{-1} at peak effect of amyl nitrite. It seems unlikely that this difference between the 2 groups was due to variation in hemodynamic alterations, because amyl nitrite induced comparable hemodynamic changes in both groups. (The mean arterial pressure-cycle length product decreased by comparable increments in both groups.)

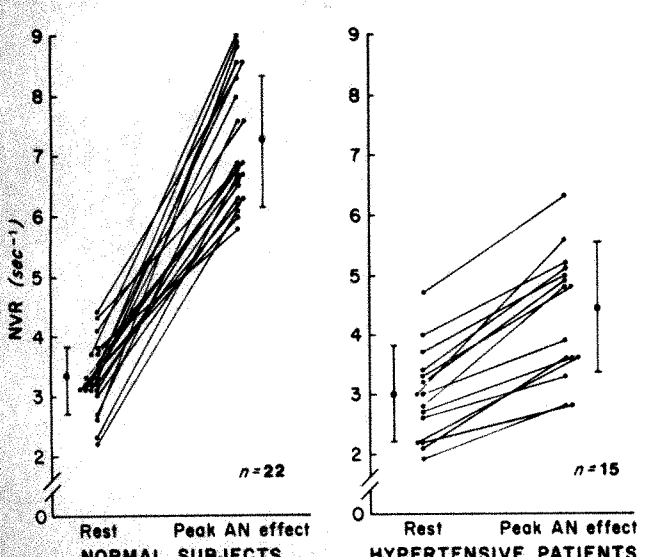

FIGURE 4. Peak effect of amyl nitrite (AN) inhalation on the normalized left ventricular relaxation velocity (NVR) in the 2 groups studied. **Bars** on both sides of the graphs depict means ± standard deviation.

The blunted response of the normalized left ventricular relaxation velocity to amyl nitrite in the borderline hypertensive group might be due to failure of normal relaxation unmasked by the more rapid left ventricular diastolic filling induced by amyl nitrite. A similar mechanism was proposed[24] to explain the increased intensity of recorded third and fourth heart sounds noted in patients with coronary heart disease given amyl nitrite. Harrison et al.[25] found a definite slowing of total isovolumic relaxation time with advancing age independent of resting heart rate. However, in the present study, age correlated poorly with the magnitude of change in the normalized left ventricular relaxation velocity induced by amyl nitrite ($r = 0.11$; $p > 0.05$). Recognizing the difference in mean ages between the two groups we looked at age as the *only* predictive variable within the linear model for normalized left ventricular relaxation velocity. Age as the only

predictor variable showed a poor correlation (r = 0.007) and could not explain the difference in response to amyl nitrite.

Implications of the study: Because hypertension affects the left ventricular myocardium uniformly, the normalized left ventricular posterior wall relaxation velocity may show the earliest measurable change of myocardial dysfunction occurring before alterations in mass or contractility are evident. Studies are currently underway to evaluate the effect of pharmacologic therapy in the treatment of borderline hypertension and its effect on this normalized left ventricular relaxation velocity. The echocardiographic amyl nitrite stress test may prove to be a simple, noninvasive tool for the detection and study of the early involvement of cardiac muscle in hypertension.

Acknowledgment

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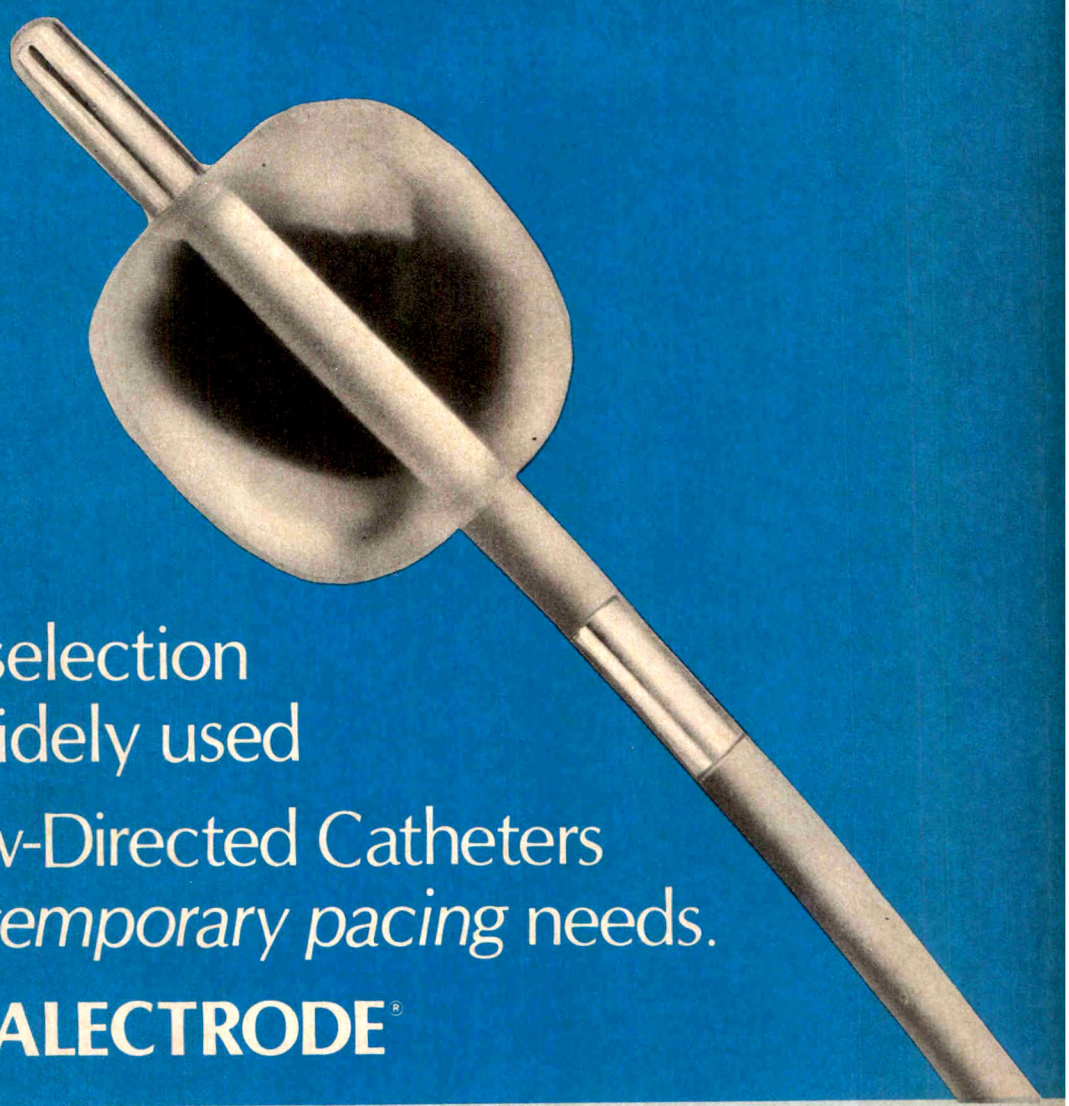

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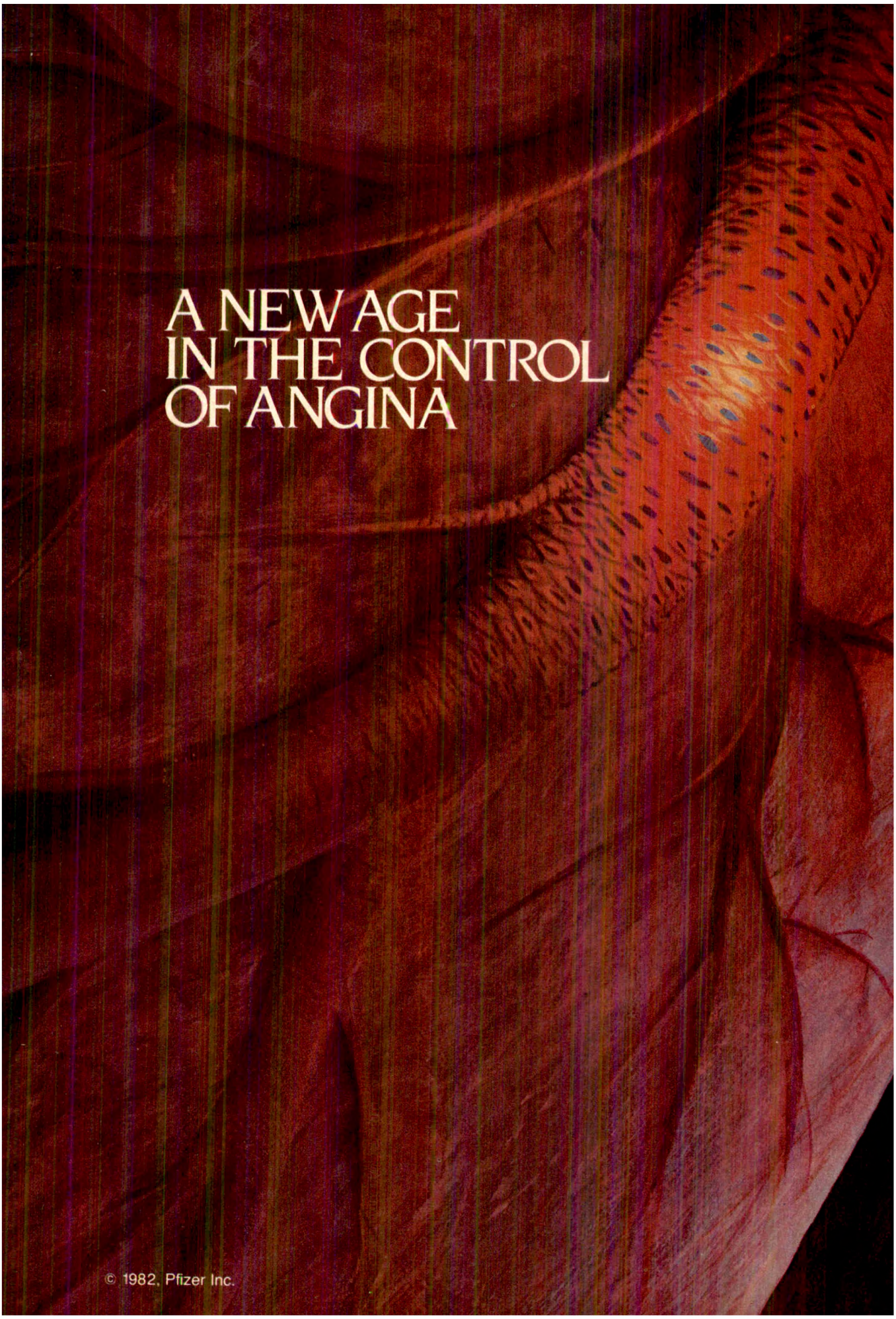

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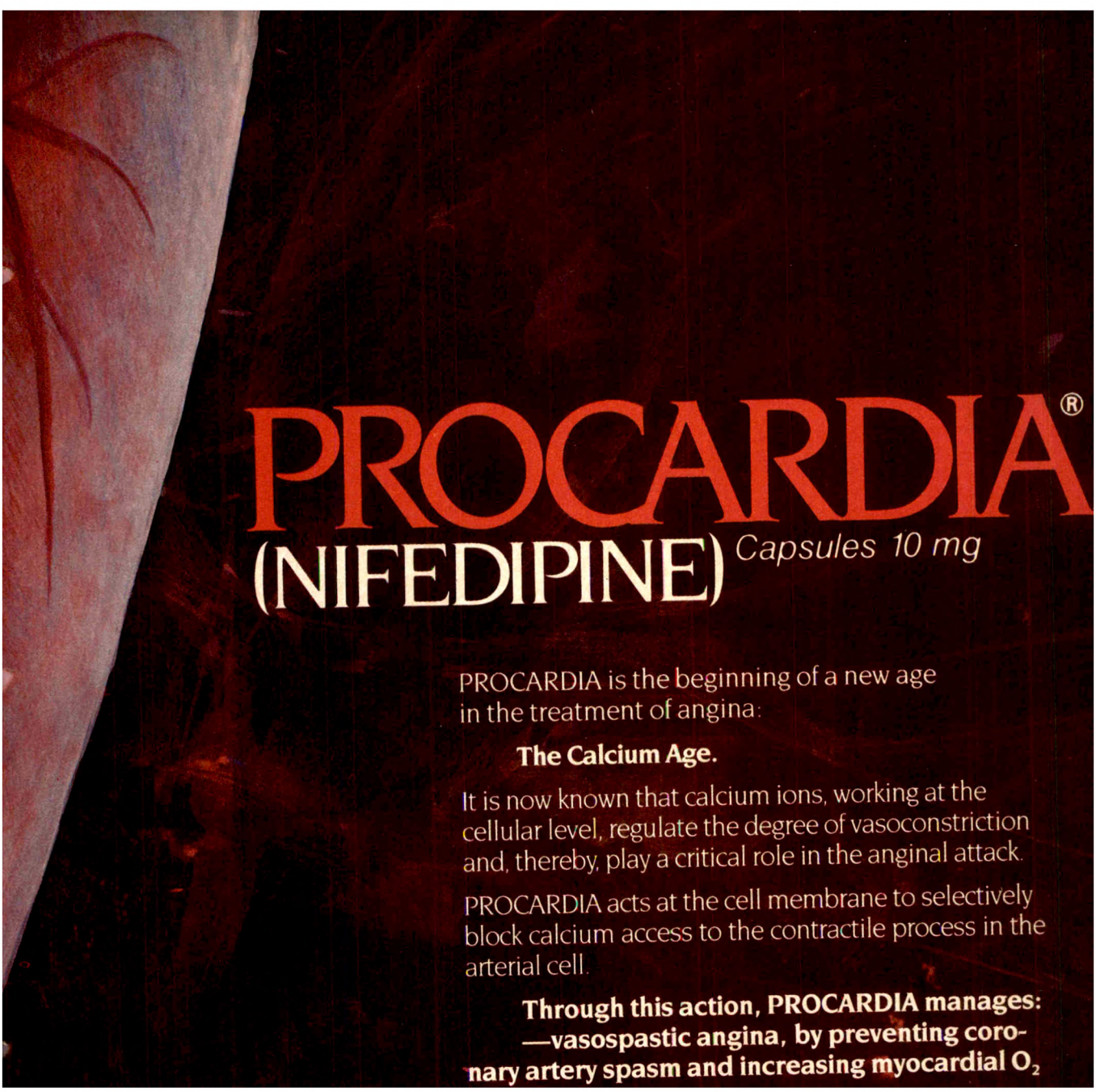
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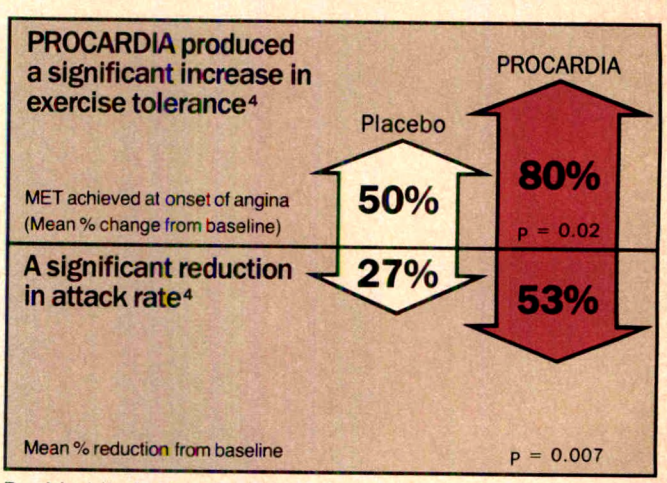
(when symptomatic despite conventional therapy)

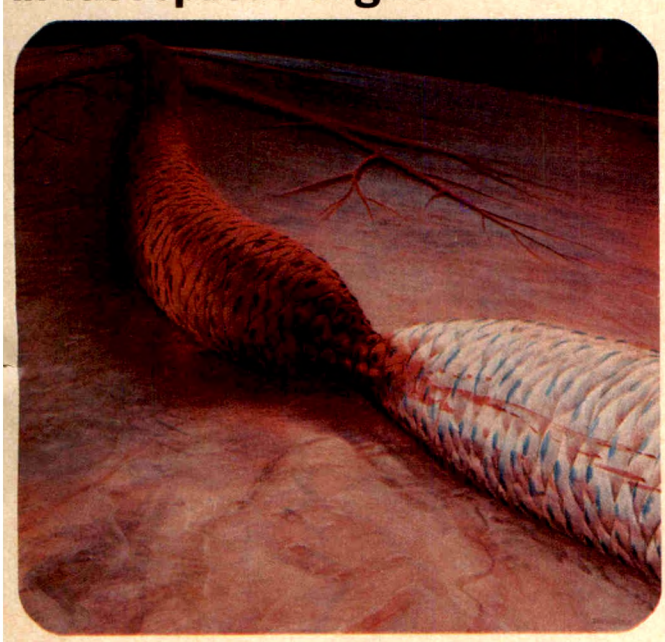


Double-blind, placebo-controlled, crossover 20-week study of 32 patients (27 evaluated for attack rate; 19 for exercise tolerance). Mean PROCARDIA dosage: 51 mg/day.

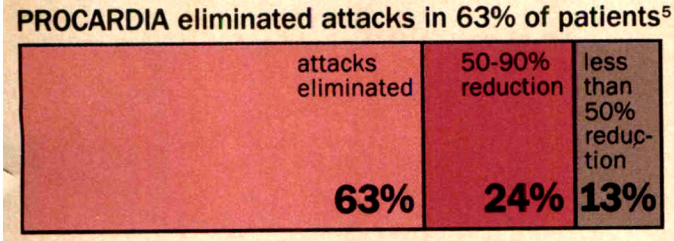
*In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Please see PROCARDIA Brief Summary on last page.

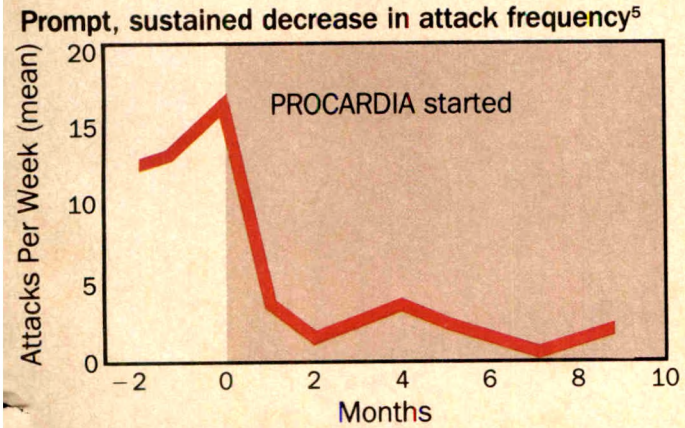
In vasospastic angina



PROCARDIA eliminated attacks in 63% of patients[5]

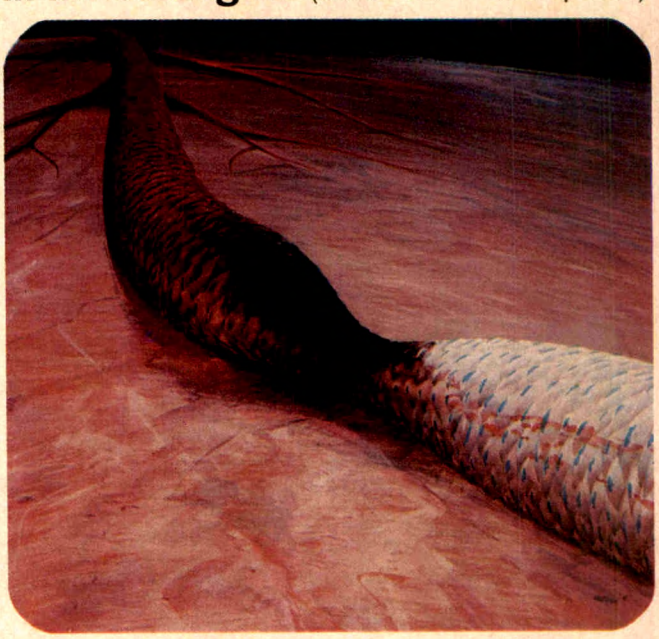


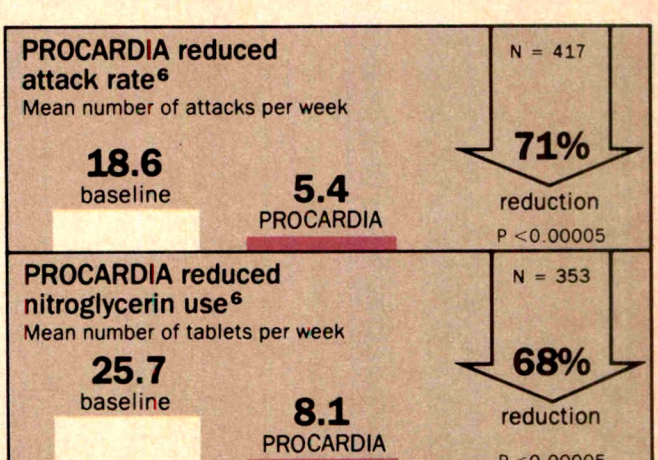
Prompt, sustained decrease in attack frequency[5]



Long-term, open study of 127 patients unresponsive to beta blockers and/or nitrates with symptoms of myocardial ischemia and demonstrated coronary artery spasm. PROCARDIA dosage: 40 to 160 mg/day.

In mixed angina (fixed lesion and spasm)





Studies of patients with mixed angina characterized by pain at rest and effort. Most patients (89%) were initiated on nitrate and/or beta blocker therapy but remained symptomatic. Minimum duration of nifedipine treatment two months. Nifedipine dosage: 30 to 120 mg/day.

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—Beta blockers can actually cause spasm. PROCARDIA prevents spasm.

—Beta blockers decrease myocardial perfusion in poststenotic areas. PROCARDIA increases myocardial perfusion to both normal and poststenotic areas.

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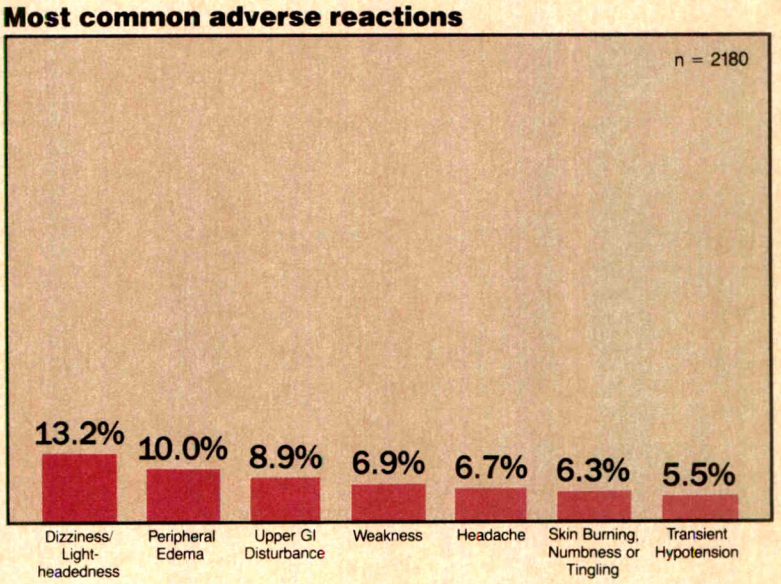

Information is drawn from a large uncontrolled experience in 2180 patients and presents the most frequent side effects reported with PROCARDIA.

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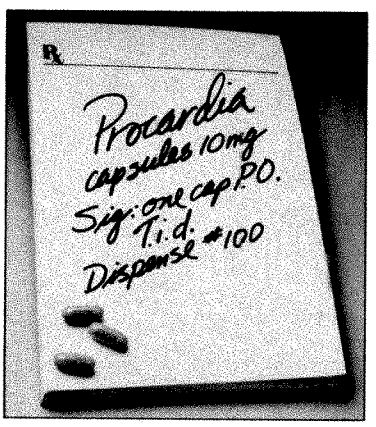

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely. Maximum dose 180 mg/day.

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(nifedipine)

BRIEF SUMMARY

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Increased Angina/Beta Blocker Withdrawal: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Pregnancy: Category C.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA Capsule contains 10 mg of nifedipine. PROCARDIA Capsules are supplied in amber glass bottles of 100 capsules (NDC 0069-2600-66).

The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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Significance of Abnormal Electrocardiograms In Highly Trained Athletes

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Electrocardiographic and other abnormalities of highly trained athletes are well recorded but not well enough known, and the more extreme changes still cause diagnostic confusion. This problem was exemplified by 10 athletes, all referred to us by cardiologists because of a diagnosis of organic heart disease. After thorough investigation, including catheter studies, all but 1 of these patients was regarded as normal and all returned to competitive sports. The criteria for diagnosing heart disease in athletes are discussed in light of the findings in 10 patients. Exercise electrocardiography and echocardiography help to exclude organic disease, but left heart catheterization is justified when doubt still exists.

For many years cardiologists have been aware that highly trained athletes may show some cardiovascular features that would be considered abnormal in an untrained person. This "athlete's heart syndrome" may include sinus or junctional bradycardia at rest, third and fourth heart sounds, systolic murmurs, a large heart on the chest radiograph, and a variety of electrocardiographic abnormalities. Despite descriptions of this cardiovascular syndrome, many athletes are still being misdiagnosed. The false trail is usually initiated by electrocardiographic findings, and with the more frequent use of the electrocardiogram in routine examinations this trend is likely to increase. The opposite aspect is equally important because people with significant heart disease may be capable of considerable sports achievement during which they may be at risk.[1,2]

Separation of normality from disease in athletes is likely to become an increasingly common problem. Over the past 4 years 10 athletes were referred to the Hammersmith and Sheffield Hospitals for assessment. All these patients had previously been seen by consultant cardiologists who had already advised them to stop training and relinquish their sporting ambitions, but had referred them for a further opinion. Because of the disruption in their lives caused by the diagnosis of heart disease, it was thought essential to perform angiographic as well as noninvasive investigations. This report contains the clinical noninvasive and catheterization data on these patients. The range of "abnormalities" is illustrated and the criteria for diagnosing organic heart disease are discussed.

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Methods

Patients: All 10 patients were athletes actively engaged in vigorous training and competition. In each patient electrocardiography had been performed, either as part of a routine examination or after some trivial complaint. In each case a cardiologist had diagnosed cardiac disease and the patient had been referred for a second opinion. All patients had been advised to stop training, 2 had received an unfavorable life insurance rating, and 1 had been refused renewal of his private pilot's license. Table I lists some relevant information about each athlete. Patient 1 is West Indian; the rest are Caucasian.

Investigations: The following investigations were performed in all patients: history, physical examination, chest radiography, resting electrocardiography, M-mode echocardiography, treadmill exercise electrocardiography using the Frank orthogonal lead system and modified Bruce protocol, and left heart catheterization with left ventricular angiography in the 45° right anterior oblique projection. In all but 2, selective coronary arteriography was performed in multiple views using the Judkins technique. Three patients underwent right heart catheterization, and in 1 patient right ventricular biopsy had been performed elsewhere.

TABLE I Referral Data on Athletes

Athlete	Weight (kg)	Age (yr)	Height (cm)	Sport	Referring Diagnosis	Reason for Initial Examination	Result of First Consultation
1	82.1	18	190	Basketball (national team)	Cardiomyopathy	Routine examination	Stopped training; stopped career in physical education
2	68.5	37	180	Competitive cycling	Uncertain	Routine examination	Stopped cycling
3	77.4	24	187	Squash	HOCM	One episode of dizziness	Stopped training
4	85.8	31	184	Judo (Olympic)	HOCM	Routine examination	Missed Olympic games
5	79.4	26	185	Football	Uncertain	Palpitation	Stopped training
6	72.5	41	177	Middle distance athlete (Olympic)	Ischemic heart disease	Life insurance	Stopped training; insurance rating
7	74.2	24	180	Tennis (professional)	Ischemic heart disease	Palpitation	Dropped from professional circuit
8	70.0	23	176	Competitive cycling	Cardiomyopathy	Life insurance	Insurance loading
9	67.8	19	175	Long distance athlete	Cardiomyopathy	Mild palpitation	Stopped running
10	71.0	26	181	Middle distance athlete	Ischemic heart disease	Routine examination	Private pilot's license refused

HOCM = hypertrophic obstructive cardiomyopathy.

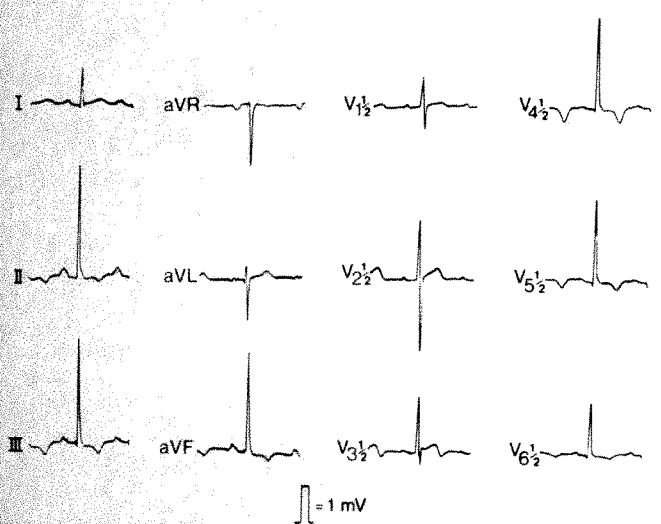

FIGURE 1. Patient 1. Electrocardiogram of international basketball player showing left ventricular hypertrophy and T-wave changes. Paper speed 25 mm/s. (Note half standardization in chest leads.)

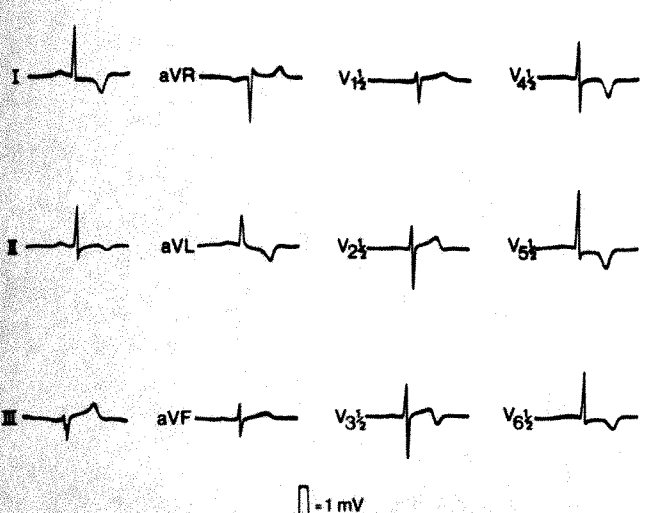

FIGURE 2. Patient 4. Electrocardiogram of Olympic judo competitor showing left ventricular hypertrophy with "strain" pattern. (Note half standardization in chest leads.)

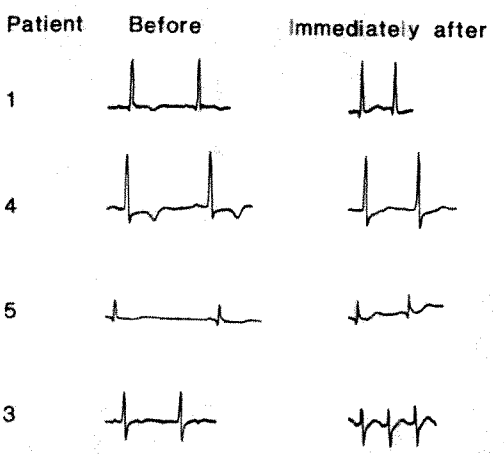

FIGURE 3. Exercise tests of Patients 1, 3, 4, and 5. Lead X (Frank orthogonal lead system) before and immediately after exercise. Paper speed 25 mm/s. Note "normalization" of preexercise T-wave inversion.

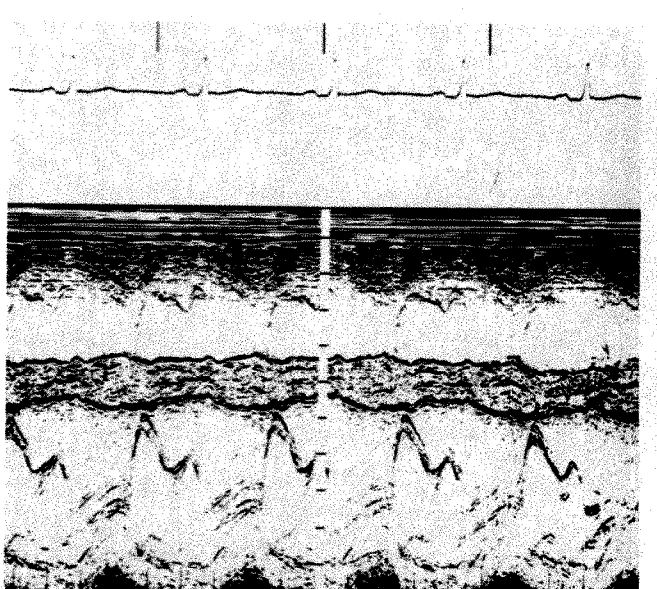

FIGURE 4. Echocardiogram of Patient 6. Note the thick septum (1.4 cm) and vigorous left ventricular posterior wall motion (0.9 cm thick). Mitral valve movement is normal. Left ventricle cavity dimensions: systolic 2.9 cm, diastolic 4.6 cm.

TABLE II Noninvasive Data

Athlete	Examination	Chest Radiography	ECG	Exercise ECG	Echocardiography
1	Systolic murmur, S_3	CTR 1:2	Gross LVH	T-wave normalization	Concentric hypertrophy
2	Palpable LV, S_4	Normal	LVH, incomplete RBBB	No change	Concentric hypertrophy
3	S_3	Normal	LVH, RAD	T-wave normalization	Septum:LVPW = 1.6:1
4	Systolic murmur, S_4	CTR 1:2	LVH	T-wave normalization	Septum:LVPW = 1.9:1
5	Normal	Normal	LVH	T-wave normalization	Normal
6	S_4	Normal	T-wave changes	No change	Normal
7	S_4, LV+	Normal	Anterior infarct	No change	Normal
8	Systolic murmur, S_4	Normal	LVH, Q-T prolongation	No change	Concentric hypertrophy
9	Normal	Normal	LVH	T-wave normalization	Normal
10	S_3, LV+	Normal	T-wave changes, LAD	No change	Normal

CTR = cardiothoracic ratio; ECG = electrocardiography; LAD = left axis deviation; LV = left ventricle; LV+ = palpable left ventricular impulse; LVH = left ventricular hypertrophy; LVPW = left ventricular posterior wall; RAD = right axis deviation; RBBB = right bundle branch block.

Results

Noninvasive Data (Table II)

Physical examination: No patient was hypertensive. A third heart sound was heard in 3 patients and a fourth sound in 5. In 3 of the 5 patients with a fourth sound an atrial impulse was palpable at the apex. A soft ejection systolic murmur was present in 3.

Chest radiography: In 2 patients the cardiothoracic ratio was at the upper limit of normal (1:2) with a left ventricular contour. All other radiographs were normal.

Electrocardiography (Fig. 1 and 2): Seven patients had left ventricular hypertrophy using standard criteria[3] and T-wave changes. Two had T wave changes only. Only 1 patient (Patient 7) had anterior Q waves suggesting previous infarction.

Exercise electrocardiography (Fig. 3): In 5 patients T-wave abnormalities became "normal" on exercise. All patients achieved heart rates in excess of 150 beats/min and their exercise capacity was outstanding. No arrhythmias were noted.

Echocardiography: Five echocardiograms were within normal limits. Three demonstrated symmetrical thickening of both septum and posterior left ventricular wall with left ventricular cavity dimensions at the upper limit of normal. One patient (Patient 3) had a septum to left ventricular posterior wall thickness ratio of 1.6:1 with no other evidence of hypertrophic cardiomyopathy (Fig. 4). Echocardiograms of 3 first degree relatives of this patient were completely normal. Patient 4 had a septum to left ventricular posterior wall thickness ratio of 1.9:1 with some systolic anterior motion of the mitral valve, but this paralleled the posterior wall and did not hit the septum. The aortic valve did not show mid-systolic closure. It was not possible to examine any of his relatives.

Cardiac Catheterization Data (Table III)

Left heart: In 5 patients the ventricular angiograms were normal, with no dyskinesia and a normal ejection fraction. In 2 the left ventricle was regarded as slightly enlarged with concentric hypertrophy of the walls, but the ejection fraction was normal. Patient 7 demonstrated definite anterior dyskinesia with good function of the remaining segments of the ventricle. In 2 patients the angiograms suggested left ventricular hypertrophy because of the vigor of contraction and prominence of the papillary muscles. In no case was the cavity bent or misshapen. In these 2 patients catheter tip transducers were inserted into the left ventricle. No outflow gradient could be measured either at rest or on provocation with amyl nitrite, isoprenaline, or extrasystoles.

Coronary arteriography disclosed that all coronary arteries were widely patent in the 8 patients examined, including Patient 7 who showed anterior Q waves and anterior wall dyskinesia. Right ventricular pressure and angiography were normal in 3 patients. Biopsy of the right ventricle had been performed elsewhere in 1 patient thought to have a congestive cardiomyopathy. This was reviewed and showed some hypertrophy of the muscle fibers with a possible slight increase in interstitial fibrosis. Neither finding was thought to be incompatible with a healthy athlete.

Discussion

On the basis of these investigations all but 1 of these 10 athletes were regarded as having a normal heart. The remaining patient (Case 7) was thought to have had a previous infarct, possibly from trauma while playing rugby football. All patients have returned to their training and competition and remain free of symptoms

TABLE III Catheterization Data

Patient	Left Ventricular Angiography	Coronary Arteriography	Right Heart Catheterization and Angiography
1	Concentric hypertrophy and dilatation	Normal	Normal (including biopsy)
2	Normal	—	—
3	Hypertrophy, no gradient	Normal	—
4	Hypertrophy, no gradient	Normal	—
5	Normal	Normal	Normal
6	Normal	Normal	—
7	Anterior dyskinesia	Normal	—
8	Hypertrophy, no gradient	—	Normal
9	Normal	Normal	—
10	Normal	Normal	—

— = not done.

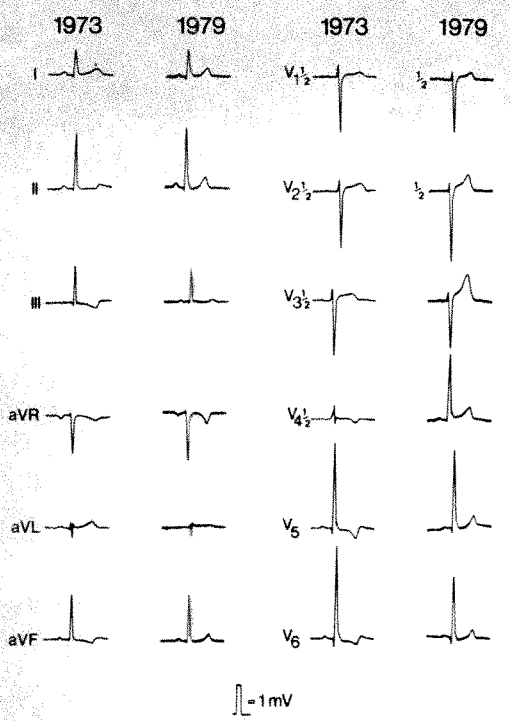

FIGURE 5. Electrocardiogram of an Olympic walker (not included in Table I) before and 6 years after cessation of training. Note drop in voltage in V_5 and V_6 and resolution of inferolateral T-wave inversions. (Note half standardization in leads V_1–V_4 in 1973 record.)

during a follow-up period of 6 months to 5 years. Two patients have had an abnormal insurance rating withdrawn and 1 has regained his private pilot's license.

Diagnostic significance of abnormal cardiovascular and electrocardiographic findings: The cardiovascular and electrocardiographic abnormalities observed in these patients are similar to those described by other investigators.[4,5] Therefore, it is not our purpose to illustrate a well-known electrocardiographic phenomenon, but rather to discuss the diagnostic significance of these changes and the problems that ensue. The referring diagnoses were hypertrophic cardiomyopathy, congestive cardiomyopathy, coronary disease, and "unknown." In this context the exercise electrocardiograms, echocardiograms, and left heart studies are of special importance.

The exercise tests in this group of athletes are interesting. "Normalization" of T-wave changes on exercise may be a false indicator of normality and in fact represent considerable repolarization abnormality.[6] Nevertheless, in most cases of ischemic heart disease, abnormal S-T and T waves become more abnormal on exertion. Less is known about the response of the electrocardiogram to exercise in patients with hypertrophic cardiomyopathy. In a study of 30 patients with hypertrophic cardiomyopathy, McKenna et al.[7] did not observe T-wave normalization on exercise, but the tests were submaximal. In a smaller series of 10 patients[8] who were exercised for a thallium stress test the S-T and T waves either stayed the same or got worse. Therefore, T-wave normalization on exertion is not a common occurrence in hypertrophic cardiomyopathy.

As with the exercise tests, echocardiography is helpful, but is likely to raise fresh doubts if appearances in athletes are not known. Echocardiographic features in athletes have been thoroughly studied, the most typical finding being an increase in left ventricular cavity dimensions and wall thickness.[4,9] Sometimes, as in Patient 4, asymmetrical hypertrophy of the septum is noted, but the distinction of physiologic and other causes of hypertrophy from hypertrophic cardiomyopathy using ultrasound is not always easy.[10–13] For this reason we would have been unable either to exclude or to diagnose hypertrophic cardiomyopathy in Patients 3 and 4 on the echocardiographic features alone.

Catheterization studies were undertaken in this selected group of athletes because their ambitions, career prospects, and finances had been adversely affected by the diagnosis of organic cardiac disease. In those patients (Cases 3 and 4) whose echocardiogram showed the most increase in wall thickness, the ventricular angiogram also showed the most hypertrophy. In neither case was the ventricular cavity misshapen as in hypertropic cardiomyopathy, nor could an intraventricular gradient be provoked. Coronary arteriography excluded coronary artery disease in all 8 patients in whom it was performed, even in the patient with anterior wall dyskinesia.

Mechanism: The mechanisms underlying the development of these changes in athletes are speculative. Electrocardiograms of the "athlete's heart" type are also seen in nonathletes, but their frequency in highly trained subjects suggests that the changes are related to the ventricular hypertrophy caused by this training. The repolarization abnormalities need further explanation especially as only a small proportion of top athletes demonstrate gross electrocardiographic "abnormalities." Interest is currently focusing on geometric factors in the left ventricle.[14,15] Maybe the end result of hypertrophy, whatever the stimulus, is governed by the ventricular muscle fiber arrangement that the patient inherited. In this case, training constitutes the stimulus and only those athletes with a particular fiber arrangement will develop hypertrophy that is asymmetrical.

Reversibility: Not much is known about the reversibility of "athlete's heart" abnormalities. All our patients are still actively training, but 1 (Table I, Case 6) did show "normalization" of T waves after several months' inactivity. We are able to report on an Olympic standard walker in whom the diagnosis of hypertrophic cardiomyopathy was made on the basis of a palpable fourth sound, systolic murmur, large heart on chest radiograph, the electrocardiographic abnormalities suggesting left ventricular hypertrophy (Fig. 5), and an echocardiogram showing moderate systolic anterior motion of the mitral valve and a septum to left ventricular free wall thickness ratio of 1.5:1. Four years later, after total cessation of training, the echocardio-

gram is normal (septum to left ventricular posterior wall thickness ratio 1.1:1) and so is the electrocardiogram. No angiograms are available, but reversibility of the hypertrophy in this patient is evident.

Clinical implications: In the final reckoning, advice to asymptomatic athletes is a matter of personal belief. An athlete who can run a mile in 3 minutes 50 seconds is not normal. Is supernormality synonymous with abnormality, and, if so, is this abnormality likely to lead to sudden decreases in cardiac output or serious ventricular arrhythmias? There are several reports of sudden death during athletic performance.[16] Maron et al.[17] studied autopsy reports of young athletes known to have died suddenly. Twenty-nine cases were collected, in 22 of which death occurred during exertion. They emphasize the frequency with which organic disease is found, the most common being hypertrophic cardiomyopathy and idiopathic concentric left ventricular hypertrophy. It is difficult to relate these findings to the clinical examination of a specific athlete, because clinical data on the athletes who died were incomplete. Sudden death in nonathletes is also encountered, although of less dramatic impact. We make every attempt to exclude coronary disease and cardiomyopathy, but even if doubt remains we encourage resumption of athletics. We believe that the diagnosis of hypertrophic cardiomyopathy should depend on the unequivocal demonstration of hypertrophy, that the diagnosis should not be based entirely on the echocardiogram, and that no other cause of hypertrophy should exist because if it does, the attribution should be to this cause such as athletics or hypertension and not to hypertrophic cardiomyopathy.

Conclusion: Although the syndrome of athlete's heart is well known, some athletes develop more marked changes than are generally recognized and diagnostic confusion results in severe disadvantage to the patient. Under these circumstances every effort, including catheterization if necessary, must be made to establish normality. Coronary disease and congestive cardiomyopathy are readily excluded, but the differential diagnosis between "supernormality" and hypertrophic cardiomyopathy may be more difficult. We advise return to competitive sport unless we can make a confident, positive diagnosis of hypertrophic cardiomyopathy. This policy has not met with problems during 5 years of follow-up study.

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Hypertrophic Nonobstructive Cardiomyopathy: A Precise Assessment of Hemodynamic Characteristics And Clinical Implications

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A precise assessment of left ventricular function was performed in 20 patients with hypertrophic nonobstructive cardiomyopathy to elucidate the basic pathophysiology, and the data were compared with those in 22 normal subjects. Whereas end-diastolic pressure was high in those with cardiomyopathy, a more accurate index of preload, end-diastolic stress, did not differ from normal value. Afterload was about half the normal value. Both isovolumic indexes [peak positive dP/dt and (dP/dt)/DP_{40}] and ejection phase indexes of contractility (ejection fraction) were in the normal range; however, the end-systolic stress volume ratio was significantly reduced (43% of the normal value). Although the left ventricular minute work index was in the normal range, the unit muscle performance (minute work/mass) was very low (49%). An abnormality of left ventricular relaxation was demonstrated by low peak negative dP/dt (56%) and prolonged time constant T (191%), and a stiff left ventricle was demonstrated by a high diastolic elastic stiffness constant (129%).

These observations suggest that the contraction of a unit muscle is inappropriate to produce an adequate contraction of the whole ventricle, and that hypertrophy might be an adaptive process to maintain normal systolic function by increasing mass and reducing afterload.

Hypertrophic cardiomyopathy has been reported to be characterized by impaired diastolic function and well-maintained systolic function.[1-3] Pump function and indexes of contractility are normal or supernormal in the majority of patients, and a hypercontractile state in the obstructive type of this disease has been emphasized, based on the facts that the intraventricular pressure gradient is increased by the administration of positive inotropic agents and preload or afterload reducing agents,[3-5] or both, and that salutary effects can be achieved by the administration of negative inotropic agents or augmentation of preload and afterload.[1,3,4]

Cardiac performance, however, consists of complex integrations of preload, afterload, contractility, relaxation, and compliance,[6-8] and normal systolic function as such does not mean that contractility is normal. Some investigators have objected to the concept of "hypercontractile state" in this disease, based on the observation of a poorly contracting interventricular septum[9,10] and the analysis of left ventricular function.[11,12] A serious question of whether contractility of the diseased heart is normal can be raised, based on a relatively characteristic histologic feature—bizarre-shaped and disarrayed myocardial cells—which has been known since Teare[13] described the first 8 cases of this disease.

Although there have been numerous reports about this disease, most recent ones are concerned with the echocardiographic findings, and studies on the basic

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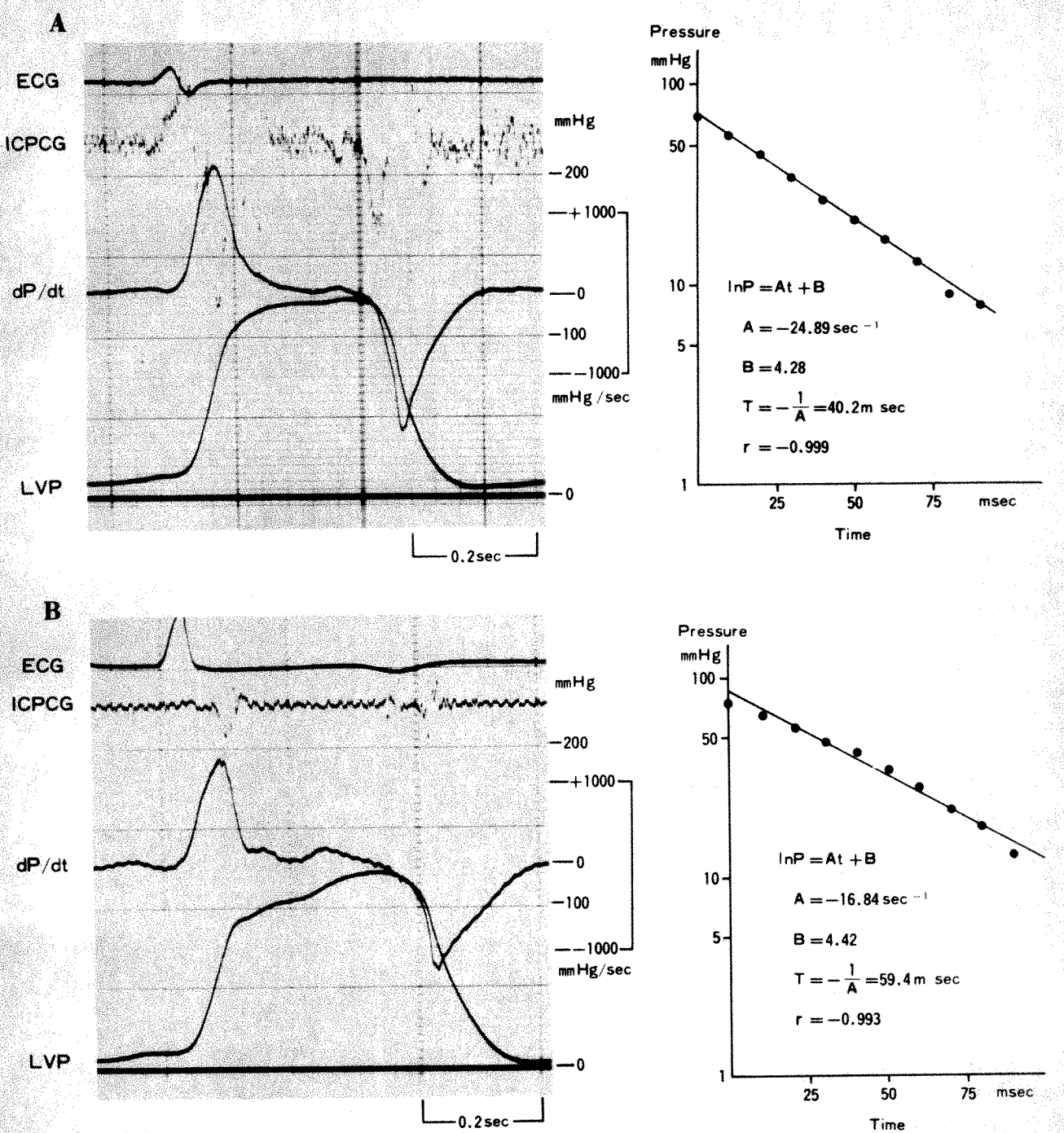

FIGURE 1. Two representative left ventricular pressure tracings. **A,** from a 42 year old man in the normal group and **B,** from a 46 year old man with apical hypertrophy. Left ventricular pressure during the isovolumic relaxation period is plotted by semilogarithmic scale on the **right** of each panel to obtain the time constant of the pressure decrease (the time constant T). The characteristics of hypertrophic cardiomyopathy, that is, low value of the maximal rate of the pressure decrease (peak negative dP/dt) and prolonged time constant T are demonstrated in **B.** A = the gradient of pressure against time; B = the intercept of pressure at time 0; ECG = electrocardiogram; ICPCG = intracardiac phonocardiogram; lnP = natural logarithm of pressure; LVP = left ventricular pressure.

pathophysiology have been limited to the obstructive type.[3] Medical and surgical treatments have focused only on this type of the disease, and the management of the nonobstructive type has been neglected even in the most recent textbook.[3] This is due partly to the fact that the basic pathophysiology of the nonobstructive type is still obscure.

This study was undertaken to evaluate left ventricular function precisely in hypertrophic nonobstructive cardiomyopathy using high fidelity pressure tracings and quantitative analyses of cineangiography, and to elucidate the basic pathophysiology in the hope that some fundamental approaches to the treatment of this disease might be established.

TABLE I Patient Groups, Left Ventricular and Aortic Pressures, Cardiac Index, and Systemic Vascular Resistance (SVR)

Group	Patients (n)	Sex	Age (yr)	HR (beats/min)	Pressure (mm Hg) LVS	LVED	AOM	AOD	CI (liters/min/m²)	SVR (dynes s cm⁻⁵)
HCM	20	16M 4F	39 ±13	68 ±9	115 ±13	14.2* ±6.7	85† ±11	99 ±14	3.03 ±1.05	1,469 ±516
NS	22	16M 6F	40 ±16	72 ±17	122 ±11	8.4 ±3.4	93 ±11	105 ±16	3.31 ±0.90	1,436 ±409

All data are expressed as mean ± 1 standard deviation of the mean.
* $p < 0.001$ compared with values in normal subjects. † $p < 0.05$ compared with values in normal subjects.
AOD = aortic dicrotic pressure; AOM = mean aortic pressure; CI = cardiac index; HCM = hypertrophic cardiomyopathy; HR = heart rate; LVED = left ventricular end-diastolic pressure; LVS = left ventricular systolic pressure; NS = normal subjects.

Methods

Study group: Among 30 patients with hypertrophic cardiomyopathy who underwent diagnostic cardiac catheterization between April 1976 and August 1980, 20 are the subjects of this study. Ten patients were excluded; 2 had the obstructive type, 1 had concomitant coronary artery disease, and high fidelity pressure tracings or cineangiograms of good quality could not be obtained in 7 cases. The diagnosis was established according to the criteria of the Study Group of Idiopathic Cardiomyopathy of Japan,[14] after modification of Goodwin's criteria.[1] Twenty-two patients who underwent catheterization for various reasons during the same period and were found to have no significant heart disease served as control subjects. Precise descriptions of the procedure of catheterization have been reported from this laboratory.[15]

Study procedure: Cardiac catheterization was performed using the brachial approach, in the fasting state and premedication with 2 mg of diazepam and 500 mg of bromovalerylurea orally, or diazepam alone, 5 mg orally. Right heart pressures were recorded with a fluid-filled system. Cardiac output was measured by the Fick or the thermodilution method. Left heart pressures were recorded in each case with a Mikro-tip® angiocatheter (model PC-471 or 481, Millar Instruments) with simultaneous recording of the first derivative of the pressure (dP/dt). Zero level was calibrated electrically by a transducer control unit (model TCB-100, Millar Instruments) before insertion of the catheter, and zero shift was adjusted at the mid-chest position through the fluid-filled system of the same catheter. Photographic recordings were obtained at paper speeds of 100 and 200 mm/s, using an 8 channel optical recording system (model 4588D, Hewlett-Packard). Five consecutive complexes in cases of normal sinus rhythm and 10 consecutive complexes in cases of atrial fibrillation (1 case in the cardiomyopathy group) were averaged for the determinations of pressure and the data derived from pressure tracings.

Angiography: Cineangiography was performed just after the pressure recordings were taken, using the same catheter in a 30° right anterior oblique projection. Thirty to 45 ml of contrast material (Angioconray®) was injected in 3 seconds by a power injector. Films were exposed at a rate of 60 frames/s with a 35 mm cine camera (Arritechno 35) mounted on a 25 cm image intensifier (Cardoscope U, Siemens). A pigtail catheter was inserted from the femoral artery, and the intraventricular pressure gradient was measured at rest and after infusion of isoproterenol, Valsalva maneuver, and postextrasystolic potentiation in all patients with hypertrophic

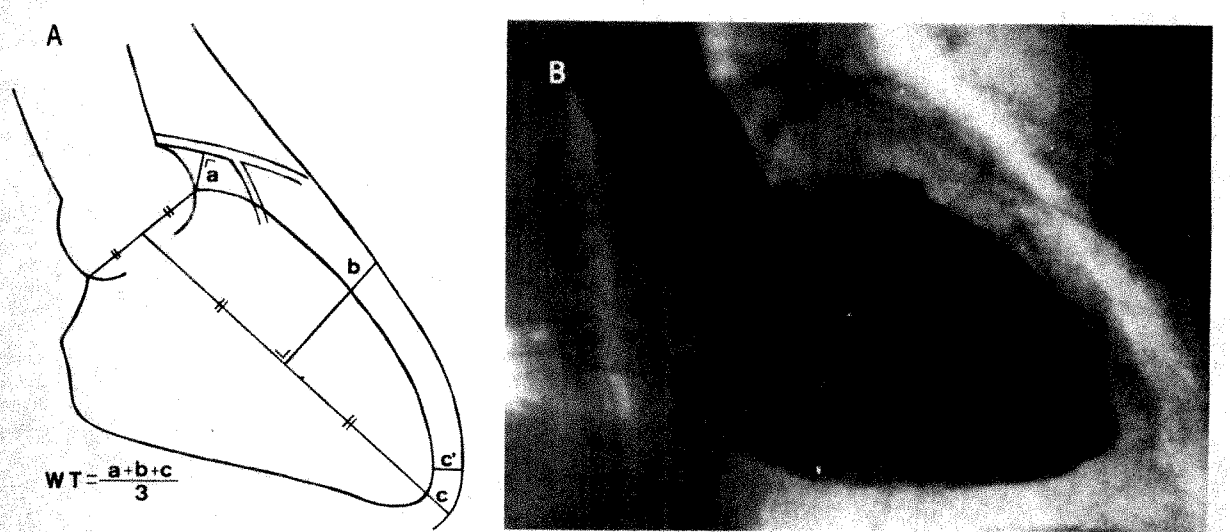

FIGURE 2. Schematic description of the calculation of the wall thickness from a drawing of the cineangiogram (**A**) and a representative cineangiogram (**B**). **A**, as disproportionate hypertrophy is a very common finding in hypertrophic cardiomyopathy, 3 points of the free wall were measured in this study at end-diastole, midsystole, and end-systole to calculate wall thickness (WT), mass, and stress. The vertical distance from the base to the left main coronary artery or the anterior descending artery (a), wall thickness at the mid-point of the anterior free wall (b), and the distance from the apex to the outer silhouette (c) were measured and averaged. As point c was difficult to identify on some occasions, the nearest well-identified point (c′) was used in such cases.

cardiomyopathy. Coronary cineangiograms were performed with the Sones' technique in all patients with hypertrophic cardiomyopathy and in the majority of normal control subjects, and were recorded in multiple projections using a 17 cm image intensifier.

Data analyses: *Two isovolumic phase indexes of contractility*, that is, the maximal rate of rise of left ventricular pressure (peak positive dP/dt) and dP/dt at the developed pressure 40 mm Hg divided by developed pressure 40 mm Hg ($[dP/dt]/DP_{40}$), and 2 indexes of relaxation, that is, the maximal rate of left ventricular pressure fall (peak negative dP/dt) and the time constant of the pressure fall (the time constant T),[16] were calculated from the pressure tracing and its first derivative (Fig. 1).

Left ventricular volumes, the short and long axes, and wall thickness were calculated at end-diastole, mid-systole, and end-systole by the area-length method of Dodge et al.,[17] using a semicomputerized system (combinations of a motion analyzer, a sonic graph pen, a microcomputer, and a graphic printer: Cardias GP 2000, Nac). There is a certain limitation in the assessment of wall thickness and the data derived from the wall thickness on cineangiography in patients with hypertrophic cardiomyopathy, because disproportionate hypertrophy such as asymmetric septal hypertrophy is a very common finding in this disease. To avoid such an inherent error as much as possible, wall thickness was measured at the base, the mid-anterior portion, and the apex in all cases (Fig. 2), and these 3 values were averaged for the calculations of wall thickness, mass, and stress. Ejection fraction (EF) was calculated by the formula: EF = EDV − ESV/EDV, where EDV is the end-diastolic volume and ESV is the end-systolic volume.

Mid-wall circumferential stress (σ) was calculated using an ellipsoid model of Mirsky's formula[18]: $\sigma = (Pb/h)[1 - (h/2B) - (B^2/2A^2)]$, where P is the pressure, A and B are the minor and major radii to the mid wall, respectively, and h is the averaged wall thickness. End-diastolic stress (σed) was calculated from the end-diastolic frame of the cineangiography and end-diastolic pressure for the determination of an accurate index of preload.[6,19] For the assessment of afterload, midsystolic stress was measured from the systolic pressure and the midsystolic frame of the cineangiogram, because the midsystolic stress has been reported to correlate significantly ($r = 0.97$) with mean systolic stress.[20] End-systolic stress was obtained from the aortic dicrotic pressure and the end-systolic frame of the film for the assessment of the contractile state by means of the end-systolic volume and pressure or stress relation.[21–25] Although the pressure was recorded during the cineangiographic procedure in all cases, the pressures just before the procedure were employed for the calculations of stress, because significant pressure distortions were almost always present because of the Valsalva maneuver during cineangiography.[12]

Left ventricular (LV) mass was calculated by the formula of Rackley et al.[26]: LV mass = $\{4/3\pi[(D + 2h)/2]^2[(L + 2h)/2] - V\} \times 1.05$, where D is the short axis, L is the long axis, h is the wall thickness, and V is the volume at the end-diastole.

The following formulas were employed for the calculation of resistance and ventricular performance: SVR = [(mean AOP − mean RAP) × k]/CO(dynes s cm^{-5}); LVMWI = (mean AOP − LV edp) × CO/BSA × 13.6 (kg·m/min per m^2), and left ventricular unit muscle minute work = LVMW/LV mass (g·m/min per g), where SVR is systemic vascular resistance, k is a constant, CO is cardiac output, AOP is aortic pressure, RAP is right atrial pressure, LVMWI is left ventricular minute work index, BSA is body surface area, and LVMW is left ventricular minute work.

TABLE II Data Derived From Left Ventricular Cineangiography

Group	LV Volume (ml/m^2) EDVI	ESVI	Mean WT at ED (mm)	LV Mass Index (g/m^2)
HCM	75 ±14	25 ±8	13.4* ±3.5	147† ±87
NS	69 ±20	25 ±9	8.8 ±1.5	77 ±29

All data are expressed as mean ± 1 standard deviation of the mean.

* $p < 0.001$ compared with values in normal subjects. † $p < 0.01$ compared with values in normal subjects.

ED = end-diastole; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; LV = left ventricular; WT = wall thickness. Other abbreviations as in Table I.

For the assessment of diastolic compliance, the diastolic elastic stiffness constant (K) was evaluated by the method of Mirsky[27]: End-diastolic elastic stiffness (g/cm^2) = Kσed + Ce, where Ce is the contractile element, $K = \delta(\alpha Ved) + (1 + \gamma)/(1 - h/2BC_1)$, $\gamma = (\alpha_1 Vw - \beta_1 V)/(\alpha_2 Vw + \beta_2 V)$, $\delta = [2 + (\gamma h/B)][1 + (h/2B) + (h^2/4B^2)] + [1 + (\gamma h/2A)][1 + (h/2A)]$, $\alpha_1 = 3 - (h/B) - (h/2A) + (h^2/2B^2)$, $\beta_1 = (h/A) + (2h/B)$, $\alpha_2 = (h/B)[1 - (h/2B) + (h^2/4B^2)] + (h/2A)[1 - (h/2A)]$, $\beta_2 = (h/B)[2 + (h^2/2B^2)] + (h/A)$, $C_1 = 1 - (B^2/2A^2)$, and $Ved = \ln(2.33\ Ped)$; where Vw is the volume of the left ventricular muscle mass, V is the ventricular volume, A and B are the short and long axes, respectively, and h is the wall thickness.

Statistics: The unpaired Student's *t* test was employed for the statistical analyses in comparing the group of patients with hypertrophic nonobstructive cardiomyopathy and the group of normal subjects. Data are presented as mean ± standard deviation.

Results

Clinical features: Among 20 patients with cardiomyopathy, 15 satisfied the echocardiographic criteria of asymmetric septal hypertrophy,[28] 2 were considered to have apical hypertrophy[29] on 2-dimensional echocardiography as well as cineangiography, and 3 showed concentric hypertrophy by these methods. All patients had no pressure gradient in the ventricle at rest, but 30 to 55 mm Hg pressure gradients were elicited after isoproterenol infusion in 3 patients with asymmetric septal hypertrophy. Three patients were symptom-free, 11 had atypical chest pain, mild dyspnea on exertion, palpitation or dizzy spells, or both, and they were considered to be in New York Heart Association[30] functional Class II. Six patients had severe symptoms of dyspnea, chest pain, and frequent episodes of paroxysmal atrial fibrillation, and 2 of them exhibited persistent atrial fibrillation during the observation period of 1 to 2 years after catheterization. One died suddenly after running 50 meters to get on a bus, and 1 had 2 documented episodes of ventricular fibrillation. There were no differences in age and sex distribution in the patients with cardiomyopathy and normal subjects (Table I).

Hemodynamic findings: By conventional measurements of pressure and cardiac output, left ventricular end-diastolic pressure was elevated in a majority of the patients with cardiomyopathy compared with

TABLE III Left Ventricular Minute Work Index, a Unit Muscle Minute Work, and End-Systolic Pressure/Volume and End-Systolic Stress/Volume Ratios

Group	LVMWI (kg·m/min/m²)	LVMW/LV Mass (g·m/min/g)	AOD/ESVI (mm Hg/ml/m²)	σes/ESVI (g/cm²/ml/m²)
HCM	3.02 ±1.30	27.5* ±19.2	4.52 ±2.07	2.82* ±1.54
NS	3.81 ±1.28	56.4 ±29.5	4.92 ±2.87 (n = 20)	6.50 ±2.56 (n = 20)

All data are expressed as mean ± 1 standard deviation of the mean.
* p <0.001 compared with values in normal subjects.
LVMW = left ventricular minute work; LVMWI = left ventricular minute work index; NS = normal subjects; σes = end-systolic stress. Other abbreviations as before.

normal subjects (mean 14.2 ± 6.7 versus 8.4 ± 3.4 mm Hg, p <0.001), with slightly lower mean aortic pressure (85 ± 11 versus 93 ± 11 mm Hg, p <0.05) (Table I). The cineangiographic characteristics of hypertrophic cardiomyopathy were a thick wall (1.34 ± 0.35 versus 0.88 ± 0.29 cm, p <0.001) and increased wall mass (147 ± 87 versus 77 ± 29 g/m², p <0.01) (Table II). Although cardiac index and left ventricular minute work index were in the normal range, the unit muscle performance estimated by left ventricular minute work/mass was about half the normal value (27.5 ± 19.2 versus 56.4 ± 29.5 g·m/min per g, p <0.001) (Tables I and III). Whereas left ventricular end-diastolic pressure was high in the group with cardiomyopathy, a more accurate index of preload, end-diastolic stress, did not differ from that of normal subjects. Afterload to the left ventricle was about half the normal value (131 ± 53 versus 270 ± 70 g/cm², p <0.001). Both isovolumic phase and ejection phase indexes of contractility were in the normal range (Table IV). A relaxation abnormality was demonstrated by lower peak negative dP/dt (1,079 ± 329 versus 1,923 ± 440 mm Hg/s, p <0.001) and prolonged time constant T (63 ± 23 versus 33 ± 8 ms, p <0.001) (Table IV). The diastolic elastic stiffness constant was significantly elevated (20.0 ± 3.8 versus 15.5 ± 2.7, p <0.001), which suggests that the left ventricle is less compliant in this disease.

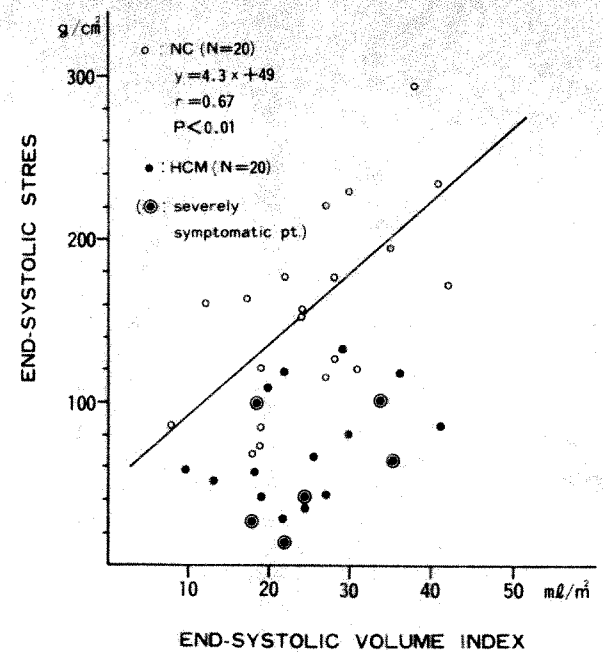

FIGURE 3. Relation between end-systolic stress and end-systolic volume index. A significant positive correlation was present between these 2 variables among the 20 normal control (NC) subjects (**open circles**) (r = 0.67, p <0.01). This observation suggests that end-systolic volume is dependent on end-systolic stress or vice versa even at rest in the normal human left ventricle. Although end-systolic volume in the 20 patients with hypertrophic cardiomyopathy (HCM) did not differ from the normal value, end-systolic stress was significantly decreased (p <0.001), and the end-systolic stress/volume ratio was shifted downward in the majority of patients (**closed circles**). This phenomenon is more apparent in 5 of the 6 severely symptomatic patients (pt.) identified as **double circles.**

Left ventricular end-systolic pressure-volume and stress-volume relations were obtained for the evaluation of the contractile state (Table III). End-systolic pressure and volume did not differ from normal values, and hence the pressure-volume ratio also did not differ between the two groups. Although there was no significant correlation between end-systolic pressure and volume among normal subjects, a significant positive correlation was present between end-systolic stress and volume in this group (Fig. 3). The end-systolic stress-volume relation was shifted downward in the cardio-

TABLE IV Indexes of Preload, Afterload, Contractility, Relaxation, and Compliance

Group	Stress (g/cm²) σed	σms	σes	EF (%)	Peak (+) dP/dt (mm Hg/s)	Peak (−) dP/dt (−mm Hg/s)	(dP/dt)/DP$_{40}$ (s^{-1})	T (ms)	K
HCM	23.8 ±11.5	131* ±53	65* ±34	67.8 ±7.2	1,510 ±343	32.9 ±7.0	1,079* ±329	63* ±23	20.0* ±3.8
NS	24.7 ±9.6	270 ±70	155 ±59	65.2 ±7.2	1,681 ±413	31.4 ±5.3	1,923 ±440	33 ±8	15.5 ±2.7

All data are expressed as mean ± 1 standard deviation of the mean.
* p <0.001 compared with values in normal subjects.
EF = ejection fraction; (dP/dt)/DP$_{40}$ = the rate of left ventricular pressure rise at developed pressure 40 mm Hg divided by developed pressure 40 mm Hg; K = diastolic elastic stiffness constant; peak (+) and (−) dP/dt = maximal rate of left ventricular pressure increase and decrease; T = time constant of the left ventricular pressure decrease; σed = end-diastolic stress as an index of preload; σms = mid-systolic stress as an index of afterload. Other abbreviations as before.

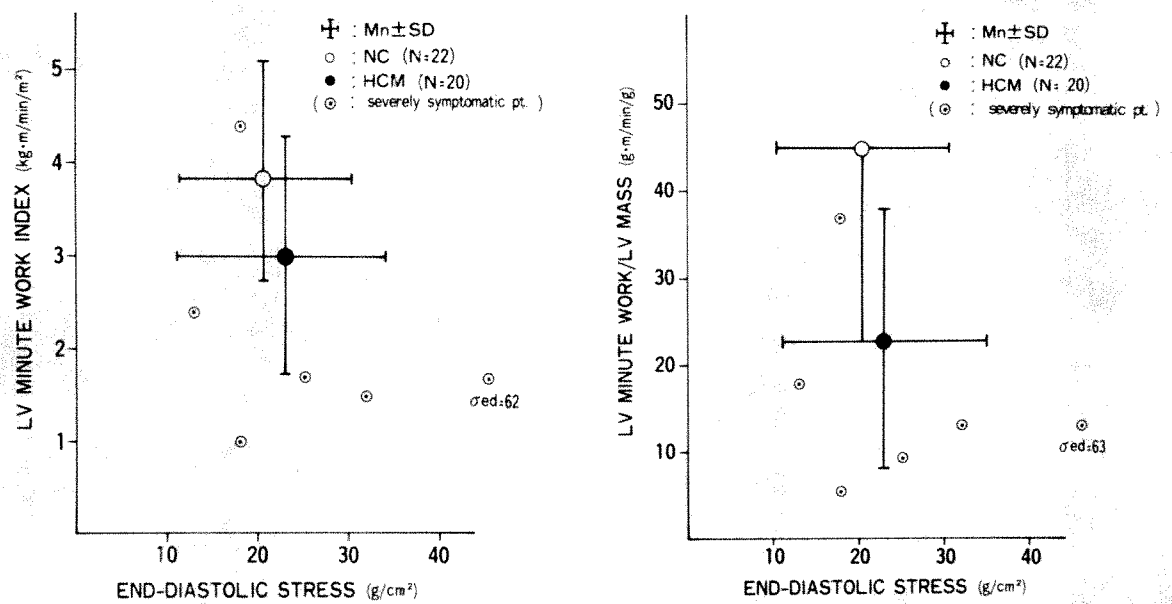

FIGURE 4. Relations between left ventricular minute work index and preload (**left**), and between a unit muscle performance and preload (**right**). **Left,** both left ventricular minute work index and preload (end-diastolic stress = σed) did not differ in patients with hypertrophic cardiomyopathy and normal subjects, indicating that patients with this disease maintain normal systolic pump function. However, the left ventricular performance in 4 of the 6 severely symptomatic patients was clearly below normal. **Right,** left ventricular unit muscle performance estimated by minute work/mass was about half the normal value ($p < 0.001$). Low performance with the same level of preload suggests that the contraction of a single muscle makes an inappropriate contribution to the contraction of the whole left ventricle. Abbreviations as in Figure 3.

myopathy group, and this ratio was significantly lower than the normal value (2.82 ± 1.54 versus 6.50 ± 2.56 g/cm²/ml per m², $p < 0.001$) (Table II).

Discussion

It is well known that cardiac performance depends on complex integrations of preload, afterload, contractility, relaxation, and compliance,[6–8] and precise assessments of these indexes are necessary for the elucidation of the basic pathophysiology of a given disease. Although recent technologic advances make it possible to obtain accurate indexes of these variables when an appropriate combination of high fidelity pressure tracing, high quality cineangiography, and computer system is employed, the majority of recent studies on hypertrophic cardiomyopathy are limited to echocardiographic observations; the basic pathophysiology of this disease is still obscure. This may be due partly to the difficulty of assessing left ventricular wall thickness and volume, and the data derived from them, because asymmetric hypertrophy of the wall and cavity obliteration are characteristic findings of this disease. Recognizing these inherent technical problems, this study was carried out in the hope that the pathophysiology of hypertrophic cardiomyopathy could be elucidated by analyzing data from an adequate number of patients. Two patients with the obstructive type were excluded from this study because left ventricular pressure was not uniform and cavity obliteration was more severe than in the nonobstructive type.

Indexes of systolic ventricular performance: In patients with cardiomyopathy, left ventricular systolic pressure, cardiac output, systemic vascular resistance, left ventricular volume, and ejection fraction did not differ from those in normal subjects. Isovolumic phase indexes of contractility were also in the normal range. This observation indicates that the systolic function is normal when it is considered as a pump. Cineangiographic characteristics were increased wall thickness and mass. As 15 of the 20 patients had echocardiographic evidence of asymmetric septal hypertrophy, wall thickness and mass calculated from the 3 points of the anterior wall may still be underestimated, and therefore stress may be overestimated.

Although end-diastolic pressure has frequently been used as an index of preload, stress at end-diastole is preferable when 2 groups of different compliance are compared.[6,19] Normal systolic pump function is demonstrated by the relation between preload and performance (Frank-Starling's relation). However, as these patients maintain normal systolic function with increased mass, a serious question is schematically shown by the relation between left ventricular unit muscle performance and preload (Fig. 4).

Afterload is defined as stress during systole, and mean systolic stress is preferable for the accurate evaluation of afterload.[6] It is time-consuming to obtain mean systolic stress, however, because it requires simultaneous measurements of ventricular pressure, volume, and wall thickness of each frame of the cineangiogram during the whole systole. Mid-systolic stress was employed here as an index of afterload because we found that this is almost identical to mean systolic stress ($r = 0.97$).[20] It was about half the normal value in hypertrophic cardiomyopathy. It is well known that the ejection phase indexes of contractility are strongly af-

fected by afterload.[6,10] Looking at the relation of these two variables, a normal ejection fraction in this disease seems to be the result of low afterload (Fig. 5). Markedly low peak systolic stress in hypertrophic cardiomyopathy has been reported by Hood et al.[31] and Gaasch et al.,[11] and the latter authors postulated depressed contractility or low afterload in this disease.

Recently, Suga and Sagawa[21] and their associates[22] proposed the end-systolic pressure-volume relation as a new index of contractility. Although this relation is independent of loading conditions, it is not preferable for the comparison of 2 different groups or diseases,[23–25] and the relation between end-systolic stress and volume is more suitable for this purpose.[23,25] Takahashi et al.[25] demonstrated a normal contractile state in mild left ventricular hypertrophy and a depressed contractile state in severe left ventricular hypertrophy associated with systemic hypertension. Among our 20 normal subjects, the relation between end-systolic stress and end-systolic volume index showed a significant correlation, and that of the patients with hypertrophic cardiomyopathy was shifted significantly downward, suggesting a depressed inotropic state in this disease.

From these observations, the following hypothesis can be derived: When contraction of a unit muscle is inappropriate to produce an adequate contraction of the whole ventricle, hypertrophy might be a "compensatory mechanism" to maintain normal systolic function. Although eccentric and concentric hypertrophy are generally considered adaptive processes for volume and pressure overload, respectively, hypertrophy in hypertrophic cardiomyopathy may be another form of compensatory mechanism.

Diastolic ventricular performance: Impaired relaxation of the left ventricle in this disease was emphasized early by Goodwin.[1] Low peak negative dP/dt was reported by Toshima et al,[32] and we[15] reported severe relaxation disturbance using peak negative dP/dt and the time constant T. Subsequent cases also showed a prolonged time constant T and low peak negative dP/dt. Although the genesis and clinical significance of this relaxation abnormality is not clear, it seems to be an important factor for the early diastolic filling disturbance because it takes about 3 times of the time constant T for the left ventricle to relax completely[33]; moreover, an early diastolic filling disturbance was reported by Matsuo et al.,[34] who measured diastolic mitral valve flow by means of the pulsed Doppler method. Acute symptomatic deterioration with the sudden onset of tachyarrhythmia is frequently observed in these patients. Whereas this phenomenon has been explained by inadequate filling of the stiff ventricle due to sudden loss of atrial contraction,[3] impaired relaxation and hence inadequate early diastolic filling may also play an important role in symptomatic deterioration with the appearance of tachyarrhythmias.

Reduced compliance or stiff left ventricle has been frequently emphasized by many investigators.[1–3,11,12,18] In the present study a high diastolic stiffness constant was demonstrated, as was reported by Mirsky.[27] In

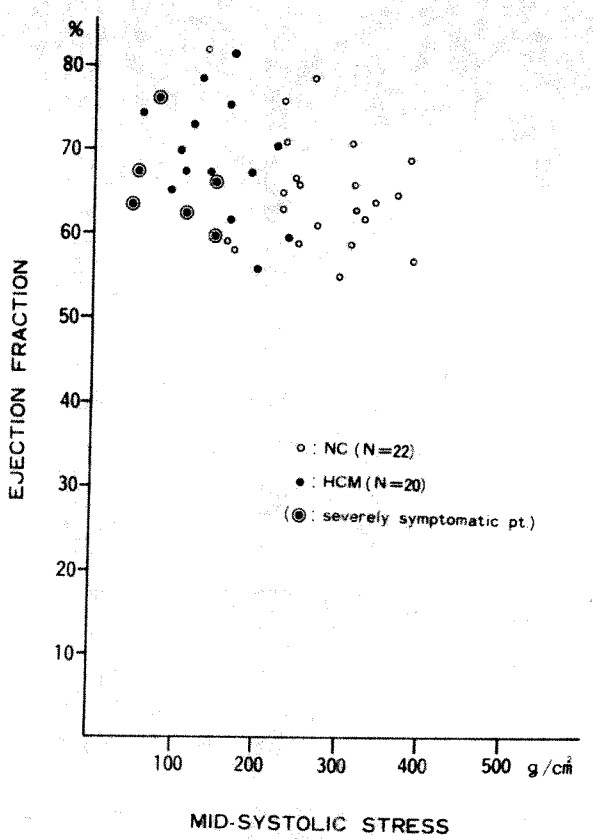

FIGURE 5. Relation between afterload and ejection fraction. Whereas there was no significant difference in ejection fraction between patients with hypertrophic cardiomyopathy and normal subjects, afterload was about half the normal value in this disease ($p < 0.001$) and this relation shifted to the left. This observation suggests that normal ejection fraction is maintained with increased mass and reduced afterload. The phenomenon was most prominent among 4 of the 6 severely symptomatic patients. Abbreviations as before.

contrast to reduced afterload in hypertrophic cardiomyopathy, afterload was normalized with increasing wall thickness in systemic hypertension.[35] Prolonged relaxation and stiff left ventricle was also demonstrated in these patients,[15,36] suggesting that concentric hypertrophy itself can result in prolonged relaxation and stiff ventricle. The degree of hypertrophy, prolonged relaxation, and stiff ventricle in systemic hypertension, however, were less severe than in hypertrophic cardiomyopathy.[36] Therefore, the important question of whether these diastolic abnormalities of hypertrophic cardiomyopathy are attributable to increased wall thickness as such or due partly to the characteristics of this disease remains unsolved.

Clinical implications: Among 20 patients with hypertrophic nonobstructive cardiomyopathy, 6 had severe symptoms. Left ventricular end-diastolic pressure was greatly elevated in 5 of these 6 patients (17 to 32 mm Hg), and the remaining patient (9 mm Hg) has had repeated episodes of paroxysmal atrial fibrillation and dyspnea during a follow-up period of 3 years, suggesting that end-diastolic pressure and hence left atrial pressure was elevated. Looking at the relation between preload and performance (Fig. 4), it is apparent

that the ventricular function in 4 of these patients was depressed. Although contractility indexes of these 6 patients were all within the normal range, the depressed systolic function in 5 of them also became apparent when the relations between afterload and ejection fraction and between end-systolic stress and volume were considered.

Several important implications for the management of patients with hypertrophic cardiomyopathy can be derived from this analysis. One patient died immediately after running to get on a bus. Whereas syncope after strenuous exercise and with the administration of preload or afterload reducing agents, or both, has been emphasized in patients with the obstructive type,[3,5] the same precautions must be taken in patients with the nonobstructive type. Although left ventricular end-diastolic pressure is elevated in the majority of these patients, preload is maintained in the normal range because of the thick-walled ventricle, and reduction of preload may not only produce syncope but also be life-threatening on some occasions. It is apparent from the Frank-Starling's curve that the sudden reduction of preload due to peripheral pooling of blood after strenuous exercise may result in life-threatening low cardiac output.

Although beta-adrenergic blocking agents are occasionally administered for the treatment of chest pain or arrhythmias, we observed acute development of dyspnea during the administration of propranolol in 3 patients in this study group as well as in 2 patients with the obstructive type who were not included in this study. The administration of such drugs may result in sudden elevation of end-diastolic pressure with reduction in cardiac output. Therefore, the administration of such drugs must be carried out with great caution.

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The Heart and Cardiac Conduction System in Polymyositis-Dermatomyositis: A Clinicopathologic Study Of 16 Autopsied Patients

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We reviewed the clinical records of 16 patients with polymyositis-dermatomyositis syndromes autopsied at The Johns Hopkins Hospital to determine the nature and extent of cardiac involvement and its correlation with the severity of disease as a whole. The adult patients ranged in age from 32 to 84 years (average 56); the 2 children were aged 2 and 10 years. The duration of disease ranged from 1 to 72 months (average 21). Seven patients had dermatomyositis, 5 had dermatomyositis with malignancy, 2 had childhood dermatomyositis, and 2 had an overlap syndrome. Seven patients had clinical evidence of congestive heart failure, 4 of whom had microscopic evidence of myocarditis. Two patients had bundle branch block; in 1 there was direct involvement of the conduction system by myositis and contraction band necrosis. Evidence of active myocarditis was present in 4 patients (25%); all had congestive failure. Focal myocardial fibrosis was present in 4 patients. Vascular alterations were present in the coronary arteries in 5 patients (31%). Three had active vasculitis, 1 had intimal proliferation, and 1 had medial sclerosis with calcification. All patients with active myocarditis had skeletal muscle involvement. Nine patients had myositis without myocarditis. There was no correlation of overall severity of the disease with the presence or absence of active myocarditis. The present study shows that cardiac involvement may be common in polymyositis; congestive failure or conduction abnormalities arising in this setting may be indicative of myocarditis.

Polymyositis may involve the heart.[1-17] The reported clinical manifestations include atrial and ventricular arrhythmias,[1,3,5-7,11,17] nonspecific ST-T wave changes,[3,4,6,7,11] conduction abnormalities,[1,3,5-7,11-15,17] left axis deviation,[6] congestive heart failure,[3,7,9,11,12] mitral valve prolapse,[17] and a hyperkinetic state.[16,17] Once thought relatively rare, clinical evidence of cardiac involvement in patients with polymyositis studied noninvasively was recently reported in as many as 52% of those with electrocardiographic abnormalities, 65% of those with mitral valve prolapse, and 76% of all those with cardiac abnormalities.[17] Pathologic studies have documented active myocarditis,[9-11] myocardial[8,11,12] and conduction system fibrosis,[12,13,15] vascular abnormalities,[11] and pericarditis.[10] The correlation of cardiac manifestations in polymyositis with overall severity of the disease in other organ systems is unknown. We reviewed the clinical and pathologic features of 16 autopsied patients with polymyositis to determine whether such a relation exists and to better define the clinical manifestations that may be used as indexes of myocardial involvement in polymyositis.

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Methods

Study cases: All cases of patients with a diagnosis of polymyositis or dermatomyositis listed in the autopsy files of The Johns Hopkins Hospital from 1889 through 1980 were reviewed. Sixteen cases satisfying the diagnostic criteria of Bohan and Peter[1] were included in the study. These are: (1) symmetrical progressive proximal muscle weakness; (2) muscle biopsy evidence of myositis; (3) elevation of serum skeletal muscle enzymes, particularly creatine kinase, but including aldolase, glutamic oxalacetic and pyruvic transaminases, and lactate dehydrogenase; (4) electromyographic evidence of myositis; and (5) dermatologic findings, including heliotrope rash, periorbital edema, erythematous dermatitis

on the dorsum of the hands (Gottron's sign), and involvement of the knees, elbows, and medial malleoli as well as the face, neck, and upper trunk. The confidence limits were defined as: definite, 3 or 4 criteria (with rash) for dermatomyositis, or 4 criteria (without rash) for polymyositis; probable, 2 criteria (with rash) for dermatomyositis, or 3 criteria (without rash) for polymyositis; and possible, 1 criterion (with rash) for dermatomyositis, or 2 criteria (without rash) for polymyositis.

The clinical records of each patient were reviewed for age, sex, race, duration of disease, and presence and duration of treatment. Clinical manifestations including muscle weakness, serum enzymes (creatine kinase, aldolase, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, and lactic acid dehydrogenase), diagnostic muscle biopsy, and electromyographic results were recorded. Associated findings including dysphagia, Raynaud's phenomenon, arthritis, pulmonary disease, and malignancy were noted.

Each case was classified into 1 of the following 5 categories of polymyositis[1,3,4]: (I) polymyositis; (II) dermatomyositis; (III) polymyositis or dermatomyositis associated with malignancy; (IV) childhood polymyositis or dermatomyositis with vasculitis; or (V) polymyositis or dermatomyositis with associated connective tissue disorder (overlap group). Electrocardiographic findings, clinical evidence of congestive heart failure, mitral valve prolapse, or hyperkinesia were recorded. No patient autopsied before 1961 met the diagnostic criteria.[1] Nine patients were autopsied in the 1960s, 4 in the 1970s, and 3 in the 1980s. Serum skeletal muscle enzyme determinations were available for 12 patients. Of the 4 in whom they were not, 2 died in the 1960s, 1 in the 1970s, and 1 in the 1980s. Electromyographic results were available in only 1 patient. In the others the presence of muscle weakness was established by physical examination. A total of 3 echocardiograms were performed, all in the same patient. Data on 12 lead electrocardiograms were available for 10 patients. Of those for whom this information was unavailable, 4 were autopsied in the 1960s and 2 in the 1970s.

Pathologic manifestations: The gross specimen of the heart was reviewed in 10 cases. Otherwise the cardiac data were taken from descriptions and measures made by the prosector at autopsy. Pathologic determinations on the heart included: heart weight, valve dimensions, chamber volumes, myocardial thickness, assessment of valvular alterations, pericardial inflammation, presence and extent of myocardial fibrosis, presence of infarcts and degree of atherosclerotic narrowing of the coronary arterial tree, and evidence of vasculitis. The conduction systems were studied by serial histologic sectioning in 11 patients using a standard technique.[18,19] Briefly, the sinoatrial node area and a large block containing the approaches and the atrioventricular node, His bundle, and proximal right and left bundles were removed. The blocks were serially sectioned at 8 μm and every 15th section was retained. Alternate slides were stained with hematoxylin and eosin, Verhoeff-van Gieson elastin stain, and other methods as indicated. At least 150 slides were prepared on each conduction system studied.

Hematoxylin and eosin-stained microscopic sections of the following organs were examined in each case: heart (average 6, exclusive of conduction system), lung (average 8), and muscle (average 6). Skin (average 2) and gastrointestinal tract (average 6) were reviewed when available. The extent, severity, and degree of activity of involvement was assessed in all heart, muscle, and skin microscopic sections according to accepted histologic criteria.[2,4] Lung and gastrointestinal sections were examined for microscopic findings suggestive of overlap syndromes.

Results

Patient Profile

Sixteen patients met the clinical diagnostic criteria described by Bohan and Peter[1] (Table I). In 11 patients the diagnosis was clinically classified as definite, in 2 as probable, and in 3 as possible. There were no patients with idiopathic polymyositis (group I), 7 with dermatomyositis (group II), 5 with dermatomyositis-polymyositis associated with malignancy (group III), 2 with childhood dermatomyositis-polymyositis with vasculitis (group IV), and 2 with an overlap syndrome (group V). The adult patients ranged in age from 32 to 84 years (average 56); the 2 children were 2 and 10 years of age. Twelve of the patients were female and 4 male. One man had dermatomyositis; the other 3 men had dermatomyositis-polymyositis with malignancy (group III). The duration of disease ranged from 1 to 72 months (average 21). Twelve patients had been treated with corticosteroids; 1 (Case 6) had received both steroids and cyclophosphamide.

Clinical Manifestations

Cardiovascular: Of the 7 patients with dermatomyositis (group II), 3 patients (Cases 1, 6, and 7) had congestive heart failure. The electrocardiogram of Patient 1, a 53 year old woman, showed left bundle branch block; in the others, the electrocardiographic changes were nonspecific. Patient 6 had high output congestive failure. An echocardiogram in this patient demonstrated an ejection fraction of 64%, a hypokinetic septum and small left ventricular cavity, dilatation of the right ventricle, and a decreased EF slope of the mitral valve (28 mm/s), with the normal being greater than 70 mm/s. The poor left ventricular function was thought to be secondary to myocardial involvement with polymyositis. One patient in the dermatomyositis group had Raynaud's phenomenon. Of the 4 patients with malignancy-associated dermatomyositis (group III), 2 (Cases 8 and 10) had congestive heart failure. One patient (Case 9), a 68 year old man, had right bundle branch block. In the others, the electrocardiographic changes were nonspecific. Both patients with childhood dermatomyositis (Group IV) had congestive heart failure; 1 patient (Case 13) had a prolonged P-R interval. Raynaud's phenomenon was present in both patients with overlap syndromes (group V). Both of these patients demonstrated features of progressive systemic sclerosis as well as polymyositis. In 1 patient (Case 16), features of polyarteritis nodosa were also present.

The direct cause of death was cardiovascular in only 3 patients. In 1 patient (Case 7) death was due to acute congestive heart failure, in 1 (Case 8) it was due to an arrhythmia occurring in the setting of congestive failure, and in another (Case 3) it was secondary to a dissecting aneurysm involving the ascending aorta, with extension into the right and left coronary arteries. No patient had evidence of hemodynamically significant valve dysfunction.

Pulmonary: Two patients had significant pulmonary involvement. One patient (Case 6) presented with

symmetric additive polyarthritis involving the hands, knees, and feet. Over the next 2 months, an erythematous malar rash as well as a heliotrope rash developed, as did a positive Gottron's sign, proximal muscle weakness, and rapidly progressive respiratory insufficiency. Despite treatment with both steroids and cyclophosphamide, ventilatory function deteriorated. Pulmonary function tests performed 10 days before death revealed a forced vital capacity (FVC) of 1.72 liters (32.9% predicted), forced expiratory volume in 1 minute (FEV_1) of 1.62 liters (36.9% predicted), FEV_1/FVC 94.3% (84% predicted), total lung capacity 2.61 liters (35.4% predicted), vital capacity 1.80 liters (34.4% predicted), functional residual capacity 1.53 liters (36.9% predicted), and residual volume 0.81 liters (38.1% predicted). The carbon monoxide diffusing capacity (D_LCO) was 4.7 ml/m/mm Hg (25.2% of predicted). Arterial blood gases on room air showed PaO_2 47 mm Hg, $PaCO_2$ 28 mm Hg, and pH 7.42 (oxygen saturation 84.8%). In this patient high output cardiac failure developed. Despite vigorous diuresis and mechanical ventilation, the patient ultimately died. Another patient (Case 15) had an overlap syndrome with features of progressive systemic sclerosis and marked interstitial fibrosis. This patient had progressive pulmonary disability and respiratory arrest at home with unsuccessful resuscitation.

Pathologic Findings

Skeletal muscle: Skeletal muscle biopsy performed during life in all cases except Patients 11 and 12 showed histologic alterations consistent with polymyositis.

TABLE I Clinical Features of 16 Patients With Polymyositis-Dermatomyositis

Patient	Age (yr)/ Race/ Sex	Duration (yr)	Class	Steroids	Muscle Weakness	Elevated Serum Enzymes	Rash	ECG	Cardiac Symptoms	Cause of Death
Group II. Dermatomyositis										
1	53/B/F	1	Def	+	+	+	+	LBBB	CHF	Sepsis
2	49/W/F	1	Def	+	+	+	+	WNL	None	Diverticulitis, sepsis
3	49/B/F	3	Def	+	+	+	+	*	None	Dissecting aneurysm
4	64/W/F	1	Def	+	+	+	+	Sinus tachy	Raynaud's	Bronchopneumonia
5	39/B/F	6	Def	+	+	+	+	*	None	Upper gastrointestinal hemorrhages
6	37/W/M	1.5	Def	+	+	+	+	NS ST-T waves;LVH	High output CHF	Respiratory failure
7	49/B/F	2	Prob	+	+	*	+	*	CHF	Pulmonary edema
Group III. Dermatomyositis with Malignancy										
8	84/W/F	0.12	Def	−	+	+	+	Sinus tachy; old post MI	CHF	Arrhythmia, adenocarcinoma of endometrium
9	68/B/M	1.5	Def	−	+	+	+	RBBB; NS ST-T waves	None	Metastatic small cell carcinoma
10	80/W/M	0.25	Def	−	+	+	+	NS ST-T waves	CHF	Transitional cell cancer of bladder; cardiogenic shock
11	65/W/F	1	Poss	+	+	*	+	*	None	Small cell carcinoma of lung; massive pulmonary hemorrhage
12	62/B/M	0.6	Poss	−	+	*	−	T-wave inversion V_1–V_2; NS ST-T waves; p-pulmonale	None	Squamous carcinoma of esophagus; bronchopneumonia
Group IV. Childhood Dermatomyositis with Vasculitis										
13	10/B/F	0.25	Def	+	+	+	+	Prolonged P-R interval	CHF	Esophageal perforation
14	2/W/F	0.25	Def	+	+	+	+	*	CHF	Respiratory failure
Group V. Overlap Syndromes										
15	53/W/F	3	Prob	+	+	+	−	Old post MI	Raynaud's	Respiratory failure
16	32/B/F	6	Poss	+	+	*	−	*	Raynaud's HBP	Sepsis, hemorrhage

* Missing data.
B = black; CHF = congestive heart failure; Def = definite; ECG = electrocardiogram; F = female; HBP = high blood pressure; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; M = male; NS ST-T waves = nonspecific ST-T wave changes; MI = myocardial infarct; Poss = possible; Prob = probable; RBBB = right bundle branch block; tachy = tachycardia; W = white; WNL = within normal limits; + = present; − = absent.

Skeletal muscle alterations were present at autopsy in 13 patients (81%). The pathologic features included lymphocytic infiltration, necrosis of muscle fibers, and variability in fiber size and staining characteristics (Fig. 1). Focal fibrosis suggestive of resolved myositis was seen in several patients. Marked regenerative activity was seen in 1 (Case 8).

Cardiovascular (Table II): The adult heart weights ranged from 190 to 690 g (average 378). No anomalies were present in the tricuspid, pulmonic, and aortic valves in any patient. In 1 patient the mitral valve showed a mild floppy change suggestive of functional prolapse; this lesion had apparently not been hemodynamically significant. Four patients had calcific mitral anulus fibrosis. All of them were in the older age group and all were female (Cases 4, 8, 11, and 15). Coronary atherosclerosis was present in 7 patients and severe in 2 (Cases 8 and 16), moderate in 2 (Cases 3 and 12), and mild in 4 (Cases 1, 4, 7, and 9). Three patients (Cases 9, 10, and 15) had remote infarcts. In Patient 9 the remote infarct was clearly related to severe coronary atherosclerosis, and this patient subsequently underwent a coronary artery bypass procedure. Patient 15 had a remote infarct in the absence of coronary atherosclerosis. This patient had systemic Raynaud's phenomenon and presumably sustained myocardial damage on the basis of cardiac Raynaud's phenomenon.[19–21] Patient 16, who also had systemic Raynaud's phenomenon and histologic features of polyarteritis nodosa, had marked arteritis of the coronary arteries and multiple recent myocardial infarcts. Patient 10 had remote and recent myocardial infarcts in the absence of atherosclerosis. Five patients with coronary atherosclerosis had received steroids. In the 3 who had not received steroids, atherosclerosis was severe in 1 (Case 9), moderate in 1 (Case 12), and mild in 1 (Case 8).

The conducting system, studied histologically in 11 patients, was abnormal in 2 (18%). One patient (Case 1) had microscopic findings consistent with direct involvement by the disease process. There was lymphocytic infiltration and fibrosis of the sinoatrial node, and contraction band necrosis and lymphocytic infiltration of the left bundle branch, which correlated with the electrocardiographic finding of left bundle branch block. One other patient (Case 7) showed attenuation of the left bundle branch, without evidence of active myocarditis. Electrocardiograms in this patient were not available. The patient with the electrocardiographic finding of right bundle branch block (Case 9) had no microscopic alteration within the conduction system.

Histologic examination of the heart in the 3 patients with clinical evidence of Raynaud's phenomenon (Cases 4, 15, and 16) revealed the myocardial changes previously described.[19–21] There was focal fibrosis

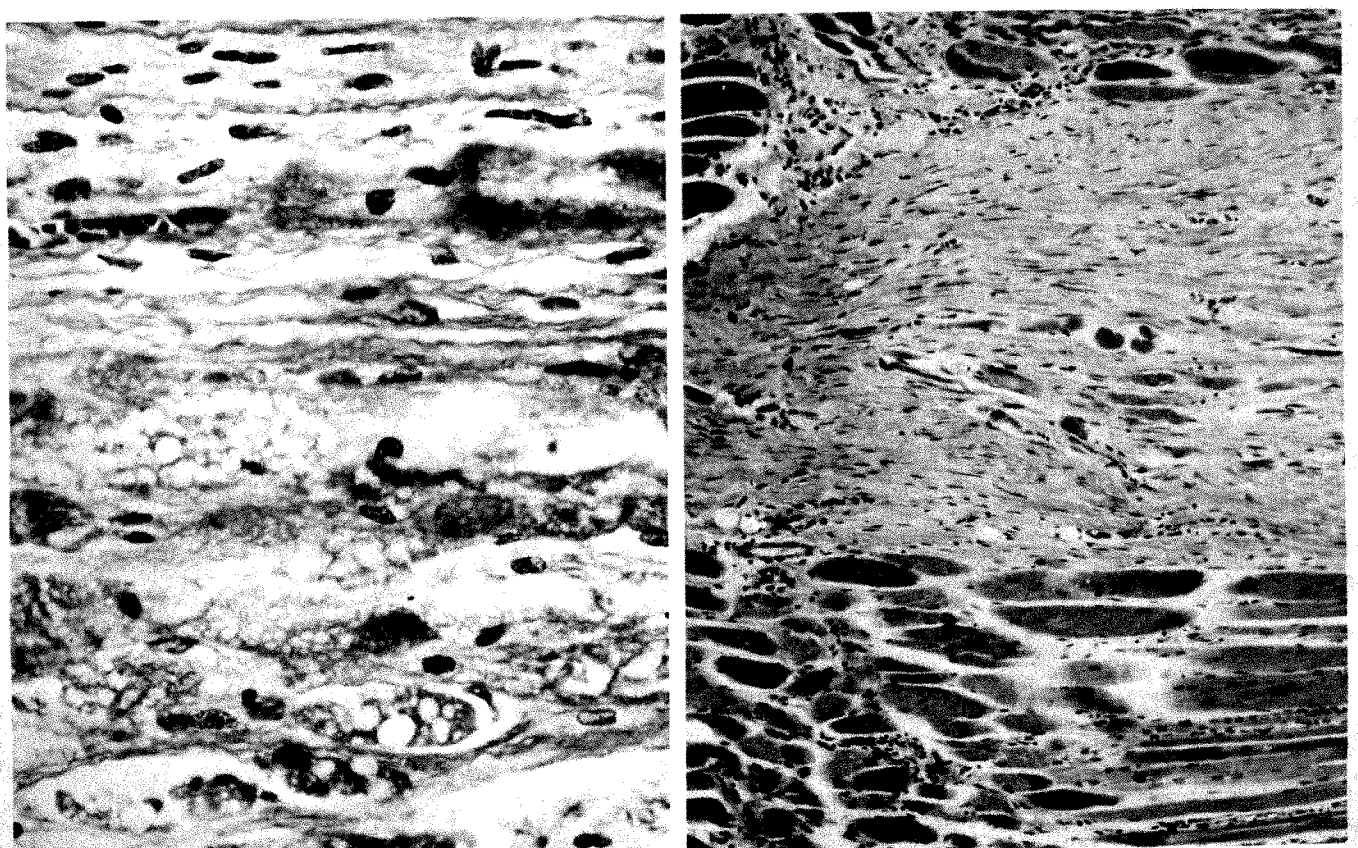

FIGURE 1. Skeletal muscle with focal replacement fibrosis (**left**) in an 84 year old woman (Case 8) and active degeneration of myocytes (**right**) in a 39 year old woman (Case 5). (Both stained with hematoxylin and eosin; **left**, magnification ×100; **right**, magnification ×500.)

TABLE II Pathologic Findings in 16 Patients With Polymyositis-Dermatomyositis

Patient	Heart			Skeletal Muscle	Lungs
	Gross	Conduction System	Myocardium		
	Group II. Dermatomyositis				
1	272 g; floppy mitral valve; focal fibrosis, left ventricle; mild coronary atherosclerosis	SAN: fibrosis, LI; AVN, His, RB: normal; LB: contraction band necrosis, LI	Interstitial myocarditis; degeneration of individual myocytes; focal fibrosis; medial sclerosis of vessels	Moderate variability in fiber size; LI; mild activity	Interstitial fibrosis and fibrosing alveolitis; edema; thromboemboli; CMV
2	400 g	*	. . .	Moderate LI, muscle destruction; mild activity	Interstitial pneumonitis; edema; fat & marrow emboli
3	430 g; moderate coronary atherosclerosis; dissecting aneurysm of aorta extending into coronary arteries	*	. . .	Mild perivascular LI	Moderate hemorrhage
4	275 g; mild CMAF; mild coronary atherosclerosis	SAN, AVN, His, RB, LB: normal	Focal fibrosis	LI, muscle degeneration; mild activity	Bronchopneumonia; edema
5	314 g	SAN, AVN, His, RB, LB: normal	. . .	LI, muscle degeneration; mild activity	Bronchopneumonia; hyaline membranes
6	460 g	SAN AVN, His, RB, LB: normal	. . .	LI; muscle destruction; marked activity	Interstitial pneumonitis & fibrosis; hyaline membranes
7	460 g; mild coronary atherosclerosis	SAN, AVN:* His, RB: normal; LB: mild attenuation	Mild chronic inflammatory infiltrate; mild contraction band necrosis	LI; mild activity	Mild hemorrhage & edema; focal granulomas
	Group III. Dermatomyositis With Malignancy				
8	190 g; moderate CMAF; mild coronary atherosclerosis	SAN, AVN, His, RB, LB: normal	Moderate to marked focal fibrosis; variability in muscle size	Marked LI; variation in muscle size; focal necrosis; myocyte regeneration; marked activity	Mild hemorrhage, edema, and organizing thromboemboli corpora amylacea
9	405; remote anteroseptal infarct; marked coronary atherosclerosis; coronary artery bypass grafts	SAN, AVN, His, RB, LB: normal	. . .	. . .	Small cell carcinoma; thromboemboli; infarct; edema
10	420 g	SAN, AVN, His, RB, LB: normal	Remote & recent infarcts, left ventricle	Marked inflammatory infiltrate & myocyte degeneration; marked activity	Metastatic transitional cell carcinoma; bronchopneumonia; emphysema; fibrosis; hemorrhage
11	260 g; CMAF	SAN, AVN, His, RB, LB: normal	. . .	. . .	Small cell carcinoma; hemorrhage; infarct; edema
12	330 g; moderate coronary atherosclerosis	SAN, AVN, His, RB, LB: normal	. . .	. . .	Emphysema; mild fibrosis; hemorrhage
	Group IV. Childhood Dermatomyositis With Vasculitis				
13	170 g	*	Mild interstitial inflammatory infiltrate	Moderate LI; active vasculitis, vascular intimal proliferation	Marked edema & purulent pleuritis; mild hemorrhage
14	60 g; probe patent foramen ovale	*	. . .	Marked LI with myocyte destruction; marked vasculitis	Marked purulent pleuritis, moderate hemorrhage & edema
	Group V. Mixed Overlap Syndromes				
15	390 g; CMAF; remote infarct, right ventricle; focal fibrosis	*	Marked proliferation, intima, coronary arteries; moderate focal fibrosis	Moderate LI; focal loss of myocytes; medial sclerosis, vessels, active	Interstitial fibrosis & pneumonitis; bronchopneumonia; edema
16	690 g; massive right atrial thrombus; marked coronary atherosclerosis	SAN, AVN, His, RB, LB: normal	Marked polyarteritis; multiple infarcts	LI & muscle destruction; marked activity	Interstitial pneumonitis; edema; hemorrhage; bronchopneumonia

* Missing data.
AVN = atrioventricular node; CMAF = calcific mitral anulus fibrosis; His = His bundle; LB = left bundle; LI = lymphocytic infiltrate; RB = right bundle; SAN = sinoatrial node.

without inflammation in 1 and marked intimal proliferation of the coronary arteries and focal fibrosis in another. The 3 patients, who also had features of polyarteritis nodosa, had marked arteritis of the coronary arteries and multiple infarcts.

Microscopic examination of the heart showed pathologic alterations attributable to involvement with a polymyositis-dermatomyositis disease process in 4 patients (25%) (Cases 1, 7, 8, and 13). These findings consisted of an interstitial inflammatory cell infiltrate, contraction band necrosis, degeneration of individual myocytes, variation in myocyte size, and focal fibrosis (Fig. 2).

All 4 patients with active myocarditis had congestive heart failure. However, congestive failure was present in a total of 7 patients (44%), 1 of whom (Case 6) had high output failure. Thus, in 25% of cases, congestive heart failure was directly attributable to myocarditis related to the underlying disease. Of the 4 patients with congestive failure secondary to polymyositis, 3 had abnormal electrocardiograms. In the other, the electrocardiographic data were unobtainable. One patient (Case 1) had left bundle branch block owing to histologically documented involvement of the left bundle (Fig. 3). Another patient (Case 8) showed sinus tachycardia and a remote posterior myocardial infarct on electrocardiography, which was not substantiated on pathologic examination. The 3rd patient (Case 13) had a prolonged P-R interval. In the other patients without histologic myocardial involvement by polymyositis-dermatomyositis the electrocardiographic findings were nonspecific (Table I).

Active myocarditis was always seen in the presence of active skeletal muscle myositis and was of comparable severity. However, 9 patients (Cases 2 to 6, 10, and 14 to 16) had skeletal muscle alterations without cardiac muscle involvement.

Focal fibrosis was present in a patchy distribution throughout the myocardium in 4 patients (25%). Two of these (Cases 14 and 15) had systemic Raynaud's phenomenon. Focal myocardial fibrosis may have arisen from coronary spasm.[19-21] In the other patients (Cases 1 and 8) coronary atherosclerosis was mild and the focal fibrosis was attributed to previous episodes of myocarditis.

Vascular changes were seen in both myocardial and skeletal muscle sections in 5 patients (31%) (*Fig. 4*). One patient (Case 1) had marked medial sclerosis of the coronary arteries associated with active myocarditis and focal fibrosis, suggesting remote injury. Both patients with childhood dermatomyositis had vascular changes. One patient (Case 13) showed active vasculitis with intimal proliferation. The other patient (Case 14) had marked active vasculitis. Both patients with overlap syndromes had vascular alterations. One patient with features of progressive systemic sclerosis (Case 13) had

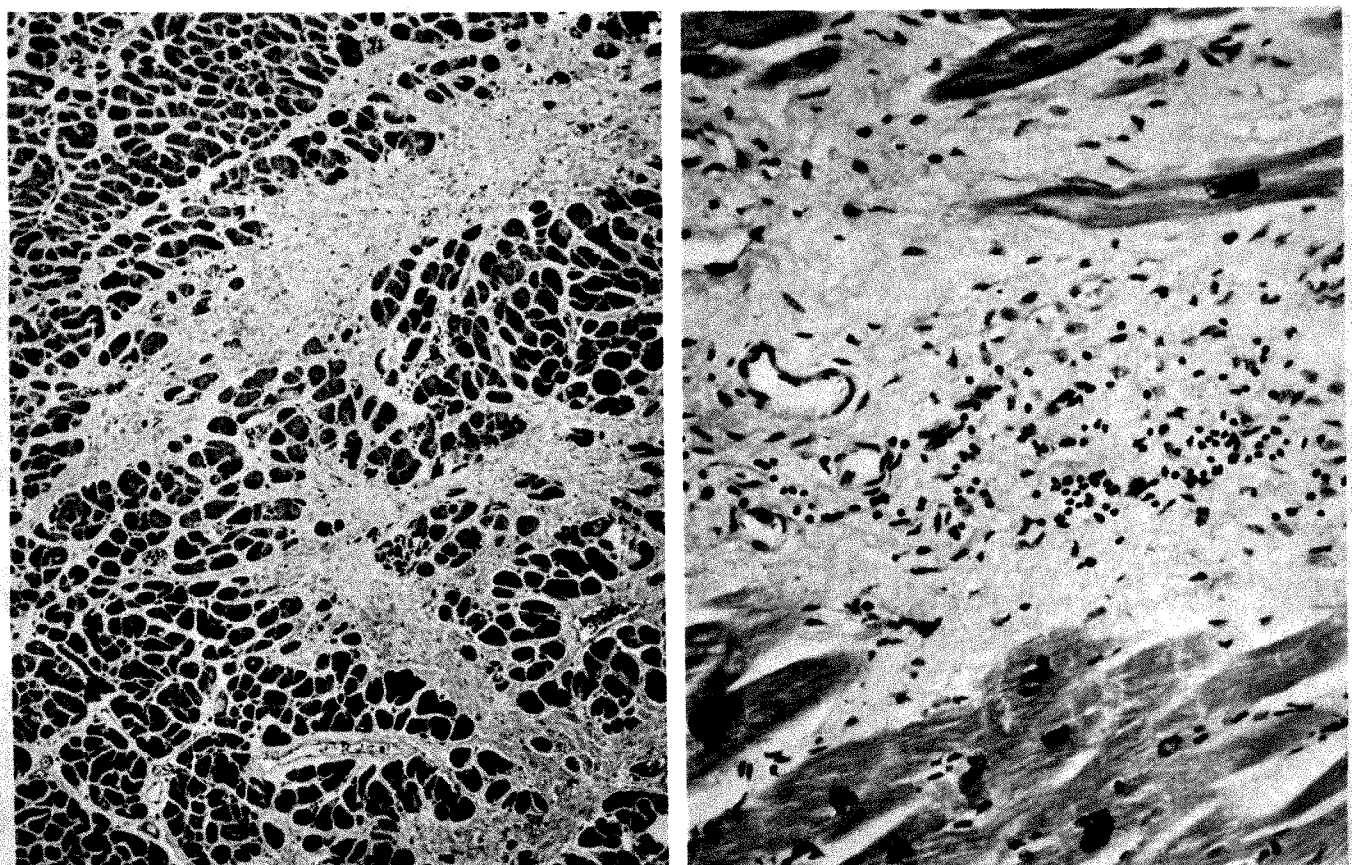

FIGURE 2. Cardiac muscle with focal replacement fibrosis (**left**) in a 64 year old woman (Case 4) and an interstitial inflammatory infiltration (**right**) in a 53 year old woman (Case 1). (Both stained with hematoxylin and eosin; **left**, magnification ×100; **right**, magnification ×500.)

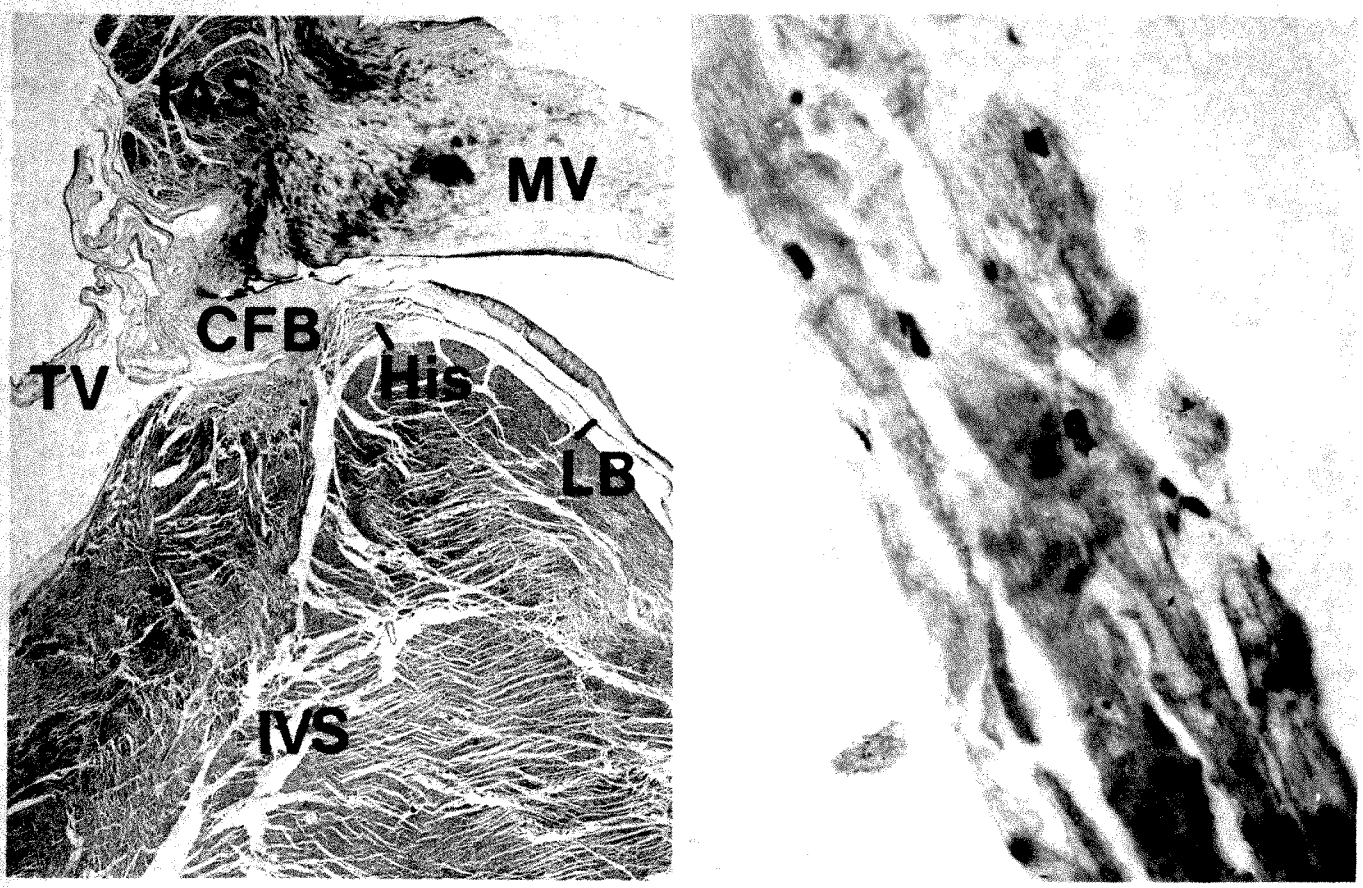

FIGURE 3. Case 1. Cardiac conduction system in a 53 year old woman with left bundle branch block. **Left,** the left bundle (LB) and distal portion of the His bundle (His). The interatrial septum (IAS) is at the **top** and the interventricular septum (IVS) **below**. The mitral (MV) and tricuspid (TV) valves are attached to the central fibrous body (CFB). **Right,** contraction band necrosis of the left bundle. The myocytes of the bundle show irregular coarse transverse condensations of sarcoplasm and their nuclei are pyknotic. (**Left,** Verhoeff-van Gieson elastin stain, magnification ×9; **right,** hematoxylin and eosin stain, magnification ×490.)

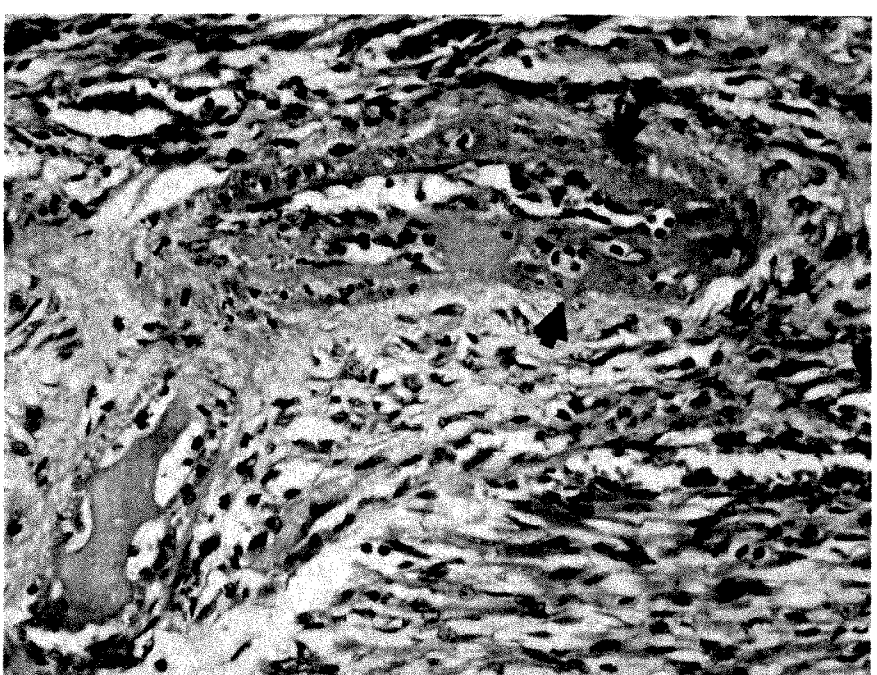

FIGURE 4. Case 14. Small artery in the skeletal muscle of a 2 year old girl with childhood dermatomyositis. There is necrosis of the portion of arterial wall between the **arrows.** (Hematoxylin and eosin stain; magnification ×250.)

typical intimal proliferation of the coronary arteries in association with focal fibrosis[19–21]; this patient had marked medial sclerosis of the skeletal muscle arteries. The other (Case 16) had marked arteritis of the coronary arteries as well as those of the gastrointestinal tract; she also had polyarteritis nodosa.

Pulmonary: Five patients had pulmonary pathologic findings typical of those described in polymyositis.[8,22–24] Two patients demonstrated marked interstitial fibrosis. In 1 (Case 6) it was associated with marked active interstitial pneumonitis and intimal proliferation within the pulmonary vessels. This patient's clinical course was dominated by respiratory failure. The other patient with marked interstitial fibrosis (Case 15) also had moderate interstitial pneumonitis. This patient fell into the overlap group with features of progressive systemic sclerosis. Patient 1 had mild interstitial fibrosis and cytomegalovirus inclusions within the lung. Patient 16, who had a syndrome with features of polymyositis, progressive systemic sclerosis, and polyarteritis nodosa, had marked interstitial pneumonitis and hyaline membranes. Patient 2 had mild interstitial pneumonitis.

Other organ systems: Six patients had gastrointestinal pathologic changes. Four (Cases 1, 6, 15, and 16) demonstrated fibrosis of the muscularis. Two (Cases 13 and 16) had vasculitis of the gastrointestinal vessels; Patient 13 had childhood dermatomyositis in which esophageal perforation with sepsis was the cause of death; Patient 16 had features of polyarteritis nodosa in other organs. One patient (Case 3) had a lymphocytic infiltrate in the muscularis of the esophagus.

Although 13 patients had clinical evidence of skin involvement, it was histologically documented at autopsy in only 4 (Cases 1, 6, 8, and 13). This discrepancy is perhaps due to the occasionally transient nature of the skin manifestations as well as to autopsy limitations that precluded sampling of the face and limbs.

Discussion

Since the classic description of Oppenheim[25] in 1899, it is recognized that polymyositis may involve the heart. Most previous reports have acknowledged that cardiac involvement occurs in polymyositis but that it is uncommon.[1–10,12–16] This study of 16 autopsied patients with polymyositis syndromes demonstrated pathologic evidence of active myocarditis in 4 (25%) and focal fibrosis in 4 (25%). These findings suggest that cardiac involvement in polymyositis and dermatomyositis is not uncommon.

Electrocardiographic and conduction system abnormalities: Previous reports have suggested that several electrocardiographic abnormalities may indicate myocardial involvement in polymyositis, including atrial and ventricular arrhythmias,[1,3,5–7,11,17] nonspecific ST-T wave changes,[3,4,6,7,11] and left axis deviation.[6] Several studies describe conduction abnormalities in the setting of polymyositis.[1,3,5–7,11–15,17] There are 3 studies with pathologic documentation of conduction system lesions.[12,13,15] Lynch[12] studied a patient with complete heart block in whom examination of the conduction system revealed extensive fibrosis. Schaumberg et al.[13] described a 26 year old patient with 2:1 atrioventricular block, with fibrous replacement of the distal 3rd of the bundle of His, the atrioventricular node, and the sinoatrial node. Lightfoot et al.[15] observed a patient with intermittent complete heart block, with marked fibrosis of both bundle branches. However, this patient also had considerable coronary atherosclerosis and narrowing of the right coronary artery. The 2 largest series, those of Denbow et al.[11] and Gottdiener et al.,[17] do not address the histologic correlation of electrocardiographic abnormalities. Our study showed pathologic alterations in 2 of the 11 conduction systems studied, but in only 1 was involvement directly attributable to polymyositis.

Congestive heart failure: Congestive heart failure has been observed in patients with polymyositis.[3,7,9,11,12] In a large clinical review of 153 patients, Bohan et al.[3] recorded a frequency of 3.3%. Nine of the 20 patients studied at autopsy by Denbow et al.[11] had previous evidence of congestive heart failure. However, these workers histologically demonstrated active myocarditis, replacement fibrosis, and small vessel disease in only 6 patients (4 with congestive heart failure and 2 without). They suggested that patients with polymyositis may have cardiomyopathy that is not apparent by light microscopy and cautioned that histologic documentation of myocardial replacement fibrosis and small vessel disease did not necessarily imply that the patient had hemodynamically significant cardiomyopathy. Congestive heart failure was present in 44% of our patients, including all 4 patients with active myocarditis. Further studies, particularly at the electron microscopic level, are needed to assess myocardial changes contributing to congestive heart failure in polymyositis. Quantitation of creatine kinase MB isoenzyme bands at peak periods of myocardial failure in these patients would also be of interest.

Coronary atherosclerosis: The coronary atherosclerosis observed in these patients may be related in part to previous steroid therapy,[26] although atherosclerosis was present in 3 patients who had not received corticosteroids. Two of these patients were in their 60s; 1 was 84 years of age. Of the 5 patients with atherosclerosis who received steroids, 1 was 32, 2 were 49, 1 was 53, and 1 was 64 years of age. The relation of dermatomyositis-polymyositis to the development of coronary atherosclerosis is unclear.

Mitral valve prolapse: This anomaly was described in patients with polymyositis by Gottdiener et al.,[17] who demonstrated echocardiographic evidence of this in 65% of 17 patients, 7 of whom had a midsystolic click. None of our patients had pathologic alterations of the mitral valve unequivocally indicative of functional prolapse. One patient (Case 7) who died in pulmonary edema did show floppy change of the mitral valve, a condition associated with prolapse.[27] This patient also had histologic evidence of myocarditis.

Hyperkinetic cardiac failure: A hyperkinetic cardiovascular state has been observed in polymyositis.[16,17] Babka and Pepine[16] studied a 40 year old man with polymyositis with hyperkinetic congestive failure documented by cardiac catheterization with left ven-

triculography. His cardiac failure was refractory to digitalis and diuretics but responded to treatment with propranolol. Autopsy revealed no histologic abnormalities of the myocardium or coronary arteries. Gottdiener et al.[17] demonstrated significantly greater cardiac performance by echocardiographic documentation of enhanced ejection phase indexes of left ventricular function in patients with polymyositis as compared with matched control patients. One patient in our study had high output congestive failure with hyperkinesia documented by echocardiography; at autopsy this heart was histologically normal.

In summary, our study demonstrated pathologic evidence of cardiac involvement in a total of 7 of 16 patients (44%). Evidence of myocardial involvement included active myocarditis, focal fibrosis, vasculitis, intimal proliferation, and medial sclerosis of vessels. Conduction system changes were present in 2 (18%) of 11 patients studied.

Implications: The correlation of myocardial damage with skeletal muscle involvement cannot be fully resolved by our study. Myocardial involvement was always seen in the presence of active skeletal muscle myositis; however, the reverse was not always true. With an appreciation of the frequency of cardiac involvement in polymyositis, future noninvasive studies may help to further delineate the association of myocarditis with myositis.

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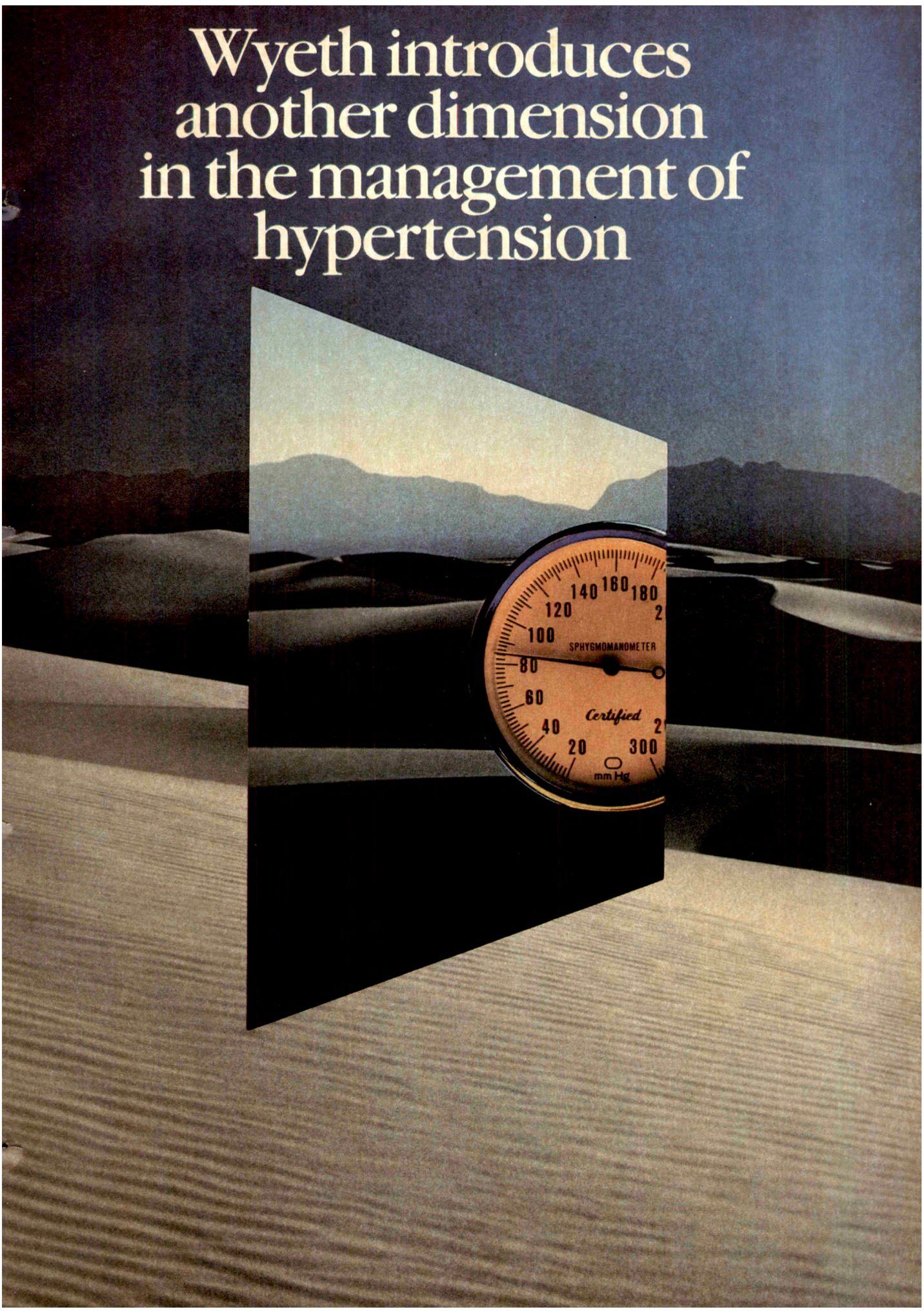
Wyeth introduces another dimension in the management of hypertension



In clinical trials to date:

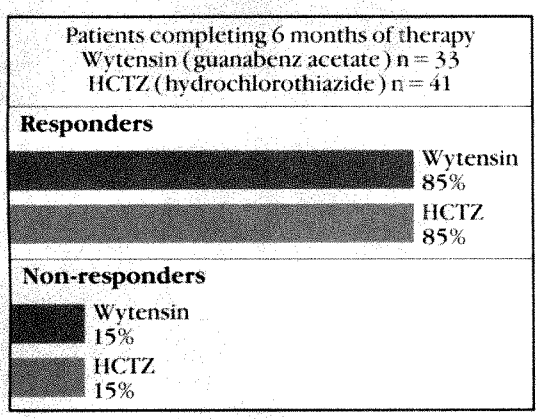
no potassium depletion
no volume depletion
no hyperlipidemia
no hyperuricemia
no hypercalcemia

no acid-base disturbances
no increased renin activity
no increased catecholamines
no azotemia
no hyperglycemia

Wyeth

Another dimension of management beyond the scope of diuretics

Highly effective in double-blind, multicenter studies



Important homeostatic advantages

	Wytensin	HCTZ
potassium	—	↓
renin	—	↑
glucose	—	↑
serum cholesterol	↓	↑
chloride	—	↓
uric acid	—	↑
calcium	—	↑
BUN	—	↑

Wytensin® did not induce long-term cardiovascular risk factors.[1]
Unlike diuretics, Wytensin can be used over the long-term without inducing atherogenic potential risk factors such as hyperlipidemia and hyperglycemia or arrhythmic risk factors such as hypokalemia. With Wytensin therapy a small decrease in heart rate and weight has been observed.

Wytensin® side effects are usually mild and transient.
Although dry mouth and/or drowsiness were the most frequently noted side effects, these subjective complaints usually diminished or disappeared over time. Only 9% of patients discontinued therapy due to drowsiness or dry mouth.
About one third of patients who started Wytensin therapy with 8 mg twice daily experienced these side effects, but starting with 4 mg b.i.d.—the recommended starting dose—reduced both the incidence of these side effects and the consequent dropout rate. In all studies to date, discontinuance of therapy for all side effects occurred in about 15% of patients.

Wytensin® may lower the price the patient pays for therapy.
Because Wytensin did not induce electrolyte and metabolic imbalance, it may save patients trouble and money. A Wytensin prescription reduces the need for frequent laboratory testing as well as for K-sparing agents or K supplements and other agents that frequently cost more than diuretics alone.

New

WyTensin®

(guanabenz acetate)

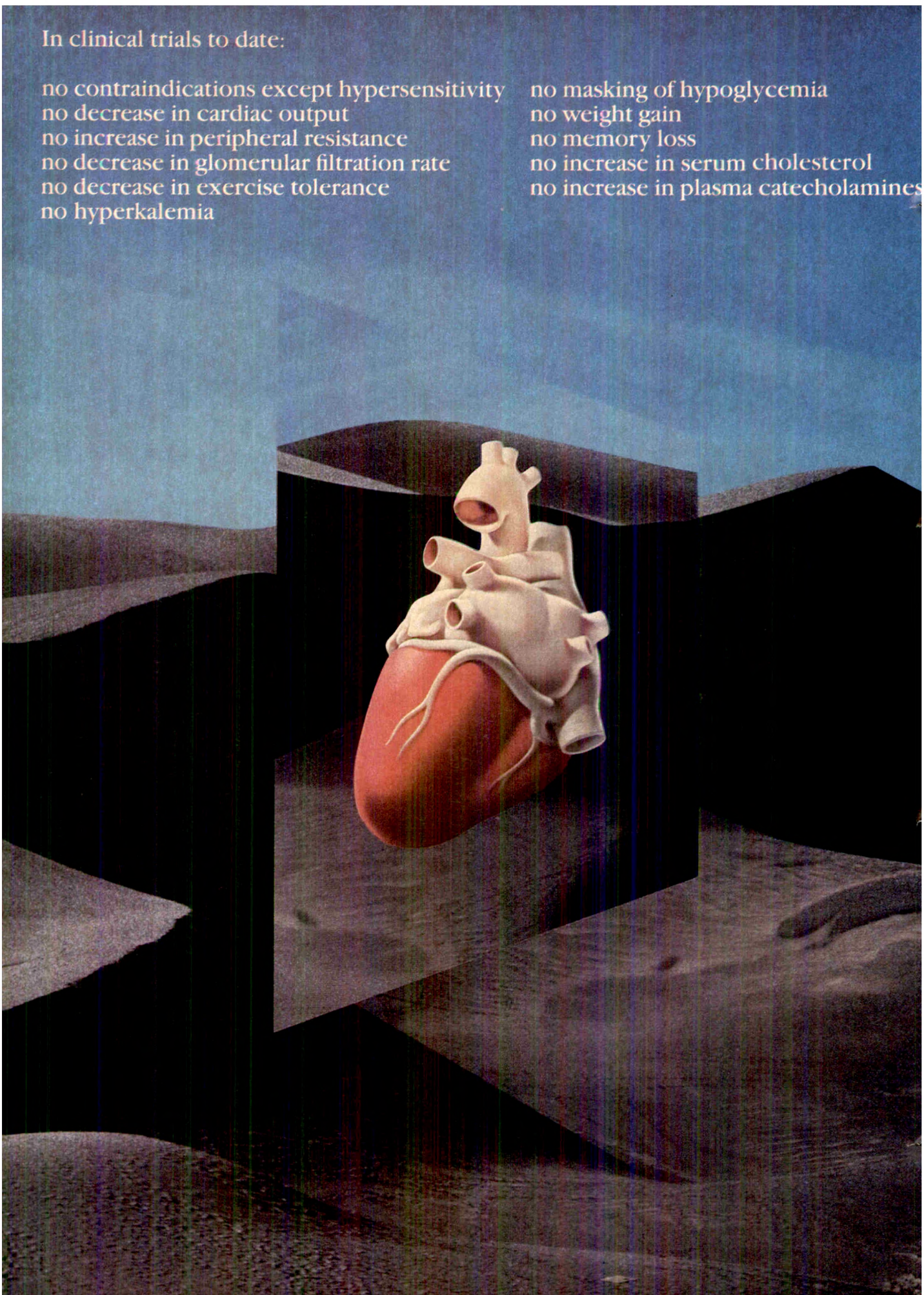
4 mg b.i.d.

Initial monotherapy in hypertension

See important information on last page.

In clinical trials to date:

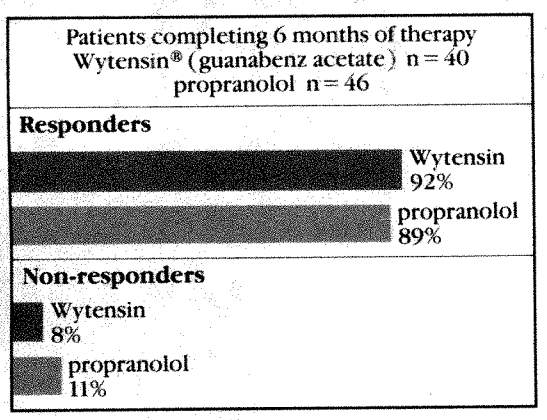
no contraindications except hypersensitivity
no decrease in cardiac output
no increase in peripheral resistance
no decrease in glomerular filtration rate
no decrease in exercise tolerance
no hyperkalemia
no masking of hypoglycemia
no weight gain
no memory loss
no increase in serum cholesterol
no increase in plasma catecholamines



Wyeth

Another dimension of management beyond the scope of beta-blockers

Highly effective in double-blind, multicenter studies



Important homeostatic advantages

	Wytensin	propranolol
potassium	—	↑
serum cholesterol	↓	—
cardiac output	—	↓
glomerular filtration rate	—	↓
peripheral resistance	↓	↑
exercise tolerance	—	↓
plasma catecholamines	↓	↑

Wytensin® lacks the risks of beta-blockade.
Wytensin® is less problematic than beta-blockers, which are contraindicated in many patients and must be used with caution in many others. For instance, exercise intolerance, nightmares, and memory failure can be problems with beta-blockers, and in many black and/or elderly patients, beta-blockade is ineffective.

Wytensin® side effects are usually mild and transient.
The subjective complaints of drowsiness and dry mouth were the most frequently noted side effects and usually diminished or disappeared over time. During initial therapy, patients should be cautioned against driving automobiles or operating dangerous machinery.

Wytensin® can be used in a broader spectrum of hypertensives.
In contrast to beta-blockers, Wytensin has no contraindications except hypersensitivity and is effective regardless of the aging process or racial factors. And, unlike beta-blockers, Wytensin causes a slight decrease in serum cholesterol and maintains potassium balance. Moreover, Wytensin does not cause clinically significant bradycardia or decreased cardiac output. There is no stimulation of vasopressor mechanisms.[2]

New

WyTensin®

(guanabenz acetate)

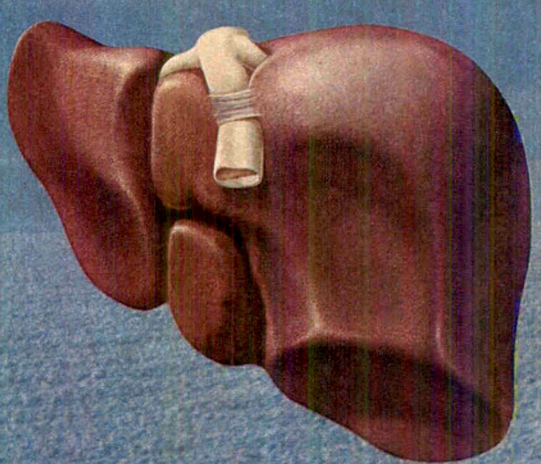
4 mg b.i.d.

Initial monotherapy in hypertension

See important information on last page.

In clinical trials to date:

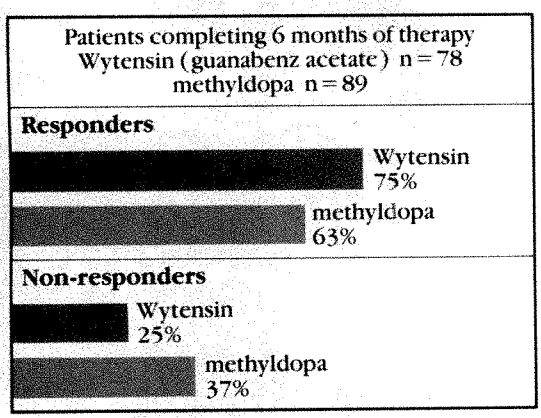
no sodium retention
no weight gain
no decrease in GFR
no immunological disturbances
no liver damage
no hemolytic anemia



Wyeth

Another dimension of management beyond the scope of methyldopa

Highly effective in double-blind, multicenter studies



Important homeostatic advantages

	Wytensin	methyldopa
sodium excretion	–	↓
plasma volume	–	↑
weight	↓	↑
glomerular filtration rate	–	↓

Wytensin® does not produce sodium retention or volume expansion.[3]
Methyldopa causes sodium retention and volume expansion with consequent development of drug tolerance. In contrast, drug tolerance has not developed with Wytensin probably because it does not induce retention of sodium and body fluid.

Wytensin® is virtually free of serious adverse reactions.
Unlike methyldopa, Wytensin does not produce immunological blood or liver toxicity or produce a positive Coombs' test. Wytensin also lacks the relatively high incidence of sexual dysfunction or mental depression seen with methyldopa.

Wytensin® side effects are often transient or avoidable.
Patients may experience drowsiness and dry mouth early during Wytensin therapy, but these effects are mostly mild, especially when the initial dosage is 4 mg b.i.d., with the second dose administered **h.s.**

New

WyTensin®

(guanabenz acetate)

4 mg b.i.d.

Initial monotherapy in hypertension

See important information on last page.

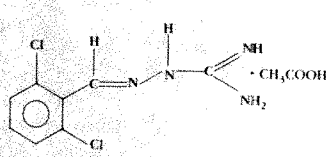
Initial monotherapy in hypertension

New Wytensin® (guanabenz acetate) 4 mg b.i.d.

More than 1,400 patients evaluated
No sodium retention
No electrolyte or metabolic risk factors
A favorable therapeutic index
Convenient, compliance-enhancing b.i.d. dosage
No contraindications except hypersensitivity

Description

Wytensin (guanabenz acetate), an antihypertensive agent for oral administration, is an aminoguanidine derivative, 2,6-dichlorobenzylideneaminoguanidine acetate, and its structural formula is:



It is an odorless, white to off-white, crystalline substance, sparingly soluble in water and soluble in alcohol, with a molecular weight of 291.14. Each tablet of Wytensin is equivalent to 4 mg or 8 mg of free guanabenz base.

Wytensin is available as 4 or 8 mg tablets for oral administration.

Clinical Pharmacology

Wytensin is an orally active central alpha-2 adrenergic agonist. Its antihypertensive action appears to be mediated via stimulation of central alpha adrenergic receptors, resulting in a decrease of sympathetic outflow from the brain at the bulbar level to the peripheral circulatory system.

PHARMACOKINETICS
In human studies, about 75% of an orally administered dose of Wytensin is absorbed and metabolized with less than 1% of unchanged drug recovered from the urine. Peak plasma concentrations of unchanged drug occur between two and five hours after a single oral dose. The average half-life for Wytensin is about 6 hours. The site or sites of metabolism of Wytensin and the consequences of renal or hepatic insufficiency on excretion of Wytensin or its metabolites have not been determined. The effect of meals on the absorption of Wytensin has not been studied.

PHARMACODYNAMICS
The onset of the antihypertensive action of Wytensin begins within 60 minutes after a single oral dose and reaches a peak effect within two to four hours. The effect of an acute single dose is reduced appreciably six to eight hours after administration, and blood pressure approaches baseline values within 12 hours of administration.

The acute antihypertensive effect of Wytensin occurs without major changes in peripheral resistance, but its chronic effect appears to be a decrease in peripheral resistance. A decrease in blood pressure is seen in both the supine and standing positions without alterations of normal postural mechanisms, so that postural hypotension has not been observed. Wytensin decreases pulse rate by about 5 beats per minute. Cardiac output and left ventricular ejection fraction are unchanged during long-term therapy.

With effective control of blood pressure in hypertensive patients, Wytensin has not demonstrated any significant effect on glomerular filtration rate, renal blood flow, renal sodium or potassium excretion, renal concentrating ability, body fluid volume, or body weight. In clinical trials of six to thirty months, hypertensive patients whose blood pressure was controlled with Wytensin lost one to four pounds of body weight. The mechanism of this weight loss has not been established. Tolerance to the antihypertensive effect of Wytensin has not been observed.

During long-term administration of Wytensin, there is a small decrease in serum cholesterol and total triglycerides without any change in the high-density lipoprotein fraction. Plasma norepinephrine, serum dopamine beta-hydroxylase, and plasma renin activity are decreased during chronic administration of Wytensin. No changes in serum electrolytes, uric acid, blood-urea nitrogen, calcium, or glucose have been observed.

Wytensin and hydrochlorothiazide have been shown to have at least partially additive effects in patients not responding adequately to either drug alone.

Indications and Usage
Wytensin is indicated in the treatment of hypertension. It may be employed alone or in combination with a thiazide diuretic.

Contraindication
Wytensin is contraindicated in patients with a known sensitivity to the drug.

Precautions
1. Sedation: Wytensin causes sedation or drowsiness in a large fraction of patients. When Wytensin is used with centrally active depressants, such as phenothiazines, barbiturates, and benzodiazepines, the potential for additive sedative effects should be considered.

2. Patients with vascular insufficiency: Wytensin, like other antihypertensive agents, should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or severe hepatic or renal failure.

3. Rebound: Sudden cessation of therapy with central alpha agonists like Wytensin may rarely result in "overshoot" hypertension and more commonly produces an increase in serum catecholamines and subjective symptomatology.

INFORMATION FOR PATIENTS
Patients who receive Wytensin should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

LABORATORY TESTS
In clinical trials, no clinically significant laboratory test abnormalities were identified during either acute or chronic therapy with Wytensin. Tests carried out included CBC, urinalysis, electrolytes, SGOT, bilirubin, alkaline phosphatase, uric acid, BUN, creatinine, glucose, calcium, phosphorus, total protein, and Coombs' test. During long-term administration of Wytensin, there was a small decrease in serum cholesterol and total triglycerides without any change in the high-density lipoprotein fraction. In rare instances an occasional non-progressive increase in liver enzymes has been observed. However, no clinical evidence of hepatic disease has been found.

DRUG INTERACTIONS
Wytensin has not been demonstrated to cause any drug interactions when administered with other drugs, such as digitalis, diuretics, analgesics, anxiolytics, and antiinflammatory or antiinfective agents, in clinical trials. However, the potential for increased sedation when Wytensin is administered concomitantly with CNS depressant drugs should be noted.

DRUG/LABORATORY TEST INTERACTIONS
No laboratory test abnormalities were identified with the use of Wytensin.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
No evidence of carcinogenic potential emerged in rats during a two-year oral study with Wytensin at doses up to 9.5 mg/kg/day, i.e., about 10 times the maximum recommended human dose. In the Salmonella microsome mutagenicity (Ames) test system, Wytensin at 200-500 mcg per plate or at 30-50 mcg/ml in suspension gave dose-related increases in the number of mutants in one (TA 1537) of five *Salmonella typhimurium* strains with or without inclusion of rat liver microsomes. No mutagenic activity was seen at doses up to those which inhibit growth in the eukaryotic microorganism, *Schizosaccharomyces pombe*, or in Chinese hamster ovary cells at doses up to those which were lethal to the cells in culture. In another eukaryotic system, *Saccharomyces cerevisiae*, Wytensin produced no activity in an assay measuring induction of repairable DNA damage. Reproductive studies showed a decreased pregnancy rate in rats administered high oral doses (9.6 mg/kg) of Wytensin, suggesting an impairment of fertility. The fertility of treated males (9.6 mg/kg) may also have been affected, as suggested by the decreased pregnancy rate of their mates, even though the females received Wytensin only during the last third of pregnancy.

PREGNANCY
Pregnancy Category C
WYTENSIN MAY HAVE ADVERSE EFFECTS ON THE FETUS WHEN ADMINISTERED TO PREGNANT WOMEN. A teratology study in mice has indicated a possible increase in skeletal abnormalities when Wytensin is given orally at doses of 3 to 6 times the maximum recommended human dose of 1.0 mg/kg. These abnormalities, principally costal and vertebral, were not noted in similar studies in rats and rabbits. However, increased fetal loss has been observed after oral Wytensin administration to pregnant rats (14 mg/kg) and rabbits (20 mg/kg). Reproductive studies of Wytensin in rats have shown slightly decreased live-birth indices, decreased fetal survival rate, and decreased pup body weight at oral doses of 6.4 and 9.6 mg/kg. There are no adequate, well-controlled studies in pregnant women. Wytensin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS
Because no information is available on the excretion of Wytensin in human milk, it should not be administered to nursing mothers.

PEDIATRIC USE
The safety and effectiveness of Wytensin in children less than 12 years of age have not been demonstrated. Therefore, its use in this age group cannot be recommended at this time.

Adverse Reactions
The incidence of adverse effects has been ascertained from controlled clinical studies conducted in the United States and is based on data from 859 patients who received Wytensin for up to 3 years. There is some evidence that the side effects are dose-related.

The following table shows the incidence of adverse effects occurring in at least 5% of patients in a study comparing Wytensin to placebo, at a starting dose of 8 mg b.i.d.

Adverse Effect	Placebo (%) n = 102	Wytensin (%) n = 109
Dry mouth	7	28
Drowsiness or sedation	12	39
Dizziness	7	17
Weakness	7	10
Headache	6	5

In other controlled clinical trials at the starting dose of 16 mg/day in 476 patients, the incidence of dry mouth was slightly higher (38%) and that of dizziness was slightly lower (12%), but the incidence of the most frequent adverse effects was similar to the placebo-controlled trial. Although these side effects were not serious, they led to discontinuation of treatment about 15% of the time. In more recent studies using an initial dose of 8 mg/day in 274 patients, the incidence of drowsiness or sedation was lower, about 20%.

Other adverse effects were reported during clinical trials with Wytensin but are not clearly distinguishable from placebo effects and occurred with a frequency of 3% or less:
Cardiovascular—chest pain, edema, arrhythmias, palpitations.
Gastrointestinal—nausea, epigastric pain, diarrhea, vomiting, constipation, abdominal discomfort.
Central nervous system—anxiety, ataxia, depression, sleep disturbances.
ENT disorders—nasal congestion.
Eye disorders—blurring of vision.
Musculoskeletal—aches in extremities, muscle aches.
Respiratory—dyspnea.
Dermatologic—rash, pruritus.
Urogenital—urinary frequency, disturbances of sexual function.
Other—gynecomastia, taste disorders.

Drug Abuse and Dependence
No reported dependence or abuse has been associated with the administration of Wytensin.

Overdosage
Accidental ingestion of Wytensin caused hypotension, somnolence, lethargy, irritability, miosis, and bradycardia in two children aged one and three years. Gastric lavage and administration of pressor substances, fluids, and oral activated charcoal resulted in complete and uneventful recovery within 12 hours in both patients.

Since experience with accidental overdosage is limited, the suggested treatment is mainly supportive while the drug is being eliminated from the body and until the patient is no longer symptomatic. Vital signs and fluid balance should be carefully monitored. An adequate airway should be maintained and, if indicated, assisted respiration instituted. There are no data available on the dialyzability of Wytensin.

Dosage and Administration
Dosage with Wytensin should be individualized. A starting dose of 4 mg twice a day is recommended, whether Wytensin is used alone or with a thiazide diuretic. Dosage may be increased in increments of 4 to 8 mg per day every one to two weeks, depending on the patient's response. The maximum dose studied to date has been 32 mg twice daily, but doses as high as this are rarely needed.

How Supplied
Wytensin® (guanabenz acetate) Tablets, Wyeth®, are available in the following dosage strengths:

4 mg, NDC 0008-0073, white, round tablet marked "WYETH" and "73", in bottles of 100.

8 mg, NDC 0008-0074, white, round, scored tablet marked "WYETH" and "74", in bottles of 100.

Keep bottles of Wytensin Tablets tightly closed.
Dispense in tight containers.
Protect from light.

Issued August 17, 1982

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Immune Reactions in Tuberculous and Chronic Constrictive Pericarditis

Clinical Data and Diagnostic Significance of Antimyocardial Antibodies

BERNHARD MAISCH, MD, STEFANIE MAISCH, MD, and KURT KOCHSIEK, MD

Humoral immune reactions were analyzed in 12 patients with exudative tuberculous pericarditis, 10 patients with constrictive pericarditis due to former tuberculosis, 10 patients with viral pericarditis, 20 patients with pulmonary tuberculosis, and 98 healthy donors. Pericarditis occurred in 12.5% of the patients with tuberculosis, whereas the incidence of tuberculosis in the 149 patients with pericarditis was 8%. Repeated pericardial puncture and pericardial effusions of greater than 500 ml with impending cardiac tamponade had to be performed in 4 patients. Clinical data indicated probable myocardial involvement in 4 of 12 patients.

Antimyolemmal antibodies, which are a muscle-specific subtype of antisarcolemmal antibodies, were found in all patients with exudative tuberculous pericarditis and viral perimyocarditis, in only 1 of 12 patients with constrictive pericarditis, and in no patient with pulmonary tuberculosis. Antifibrillary antibodies—primarily of the antimyosin type—were missed in patients with viral heart disease but were demonstrated in 75% of patients with tuberculous pericarditis.

Only sera with complement-fixing antimyolemmal antibodies of the IgG type in titers greater than 1:40 induced cytolysis of vital adult heterologous cardiocytes isolated and enriched by silica sol gradient centrifugation. These findings suggest not only that antimyolemmal antibodies are diagnostic indicators of perimyocardial involvement in tuberculous pericarditis, but also that they may play a significant role in its pathogenesis.

In a number of chronic bacterial infections, including chronic granuloma-forming diseases such as mycobacterial infections, evidence of an immunologic basis for clinical manifestations has been accumulated. In infections by Mycobacterium leprae, cellular immune reactions are positively[1] and humoral antibody levels are negatively related to the clinical spectrum[2] or to the severity of clinical manifestations of leprosy.[3,4] In tuberculosis, humoral antibody levels are also inversely proportional to the variables of cell-mediated immunity,[5–7] whereas some manifestations such as erythema nodosum are most likely mediated by immune complexes[8] or may be HLA-linked.[9] Neither humoral nor cellular immune reactions have been investigated in patients with pericardial manifestations of tuberculosis.

A 5 year follow-up study was performed to investigate clinical manifestations and humoral immune reactions in patients with tuberculosis pericarditis and compare their immunologic effector mechanisms with those in patients with viral perimyocarditis,[10–12] in patients with pulmonary tuberculosis alone, and in healthy subjects.

Methods

Patients and sera: The sera of 12 patients with exudative tuberculous pericarditis and of 10 patients with constrictive pericarditis (the underlying cause of which was previously tuberculous pericarditis) were compared with the sera of 20 patients with pulmonary tuberculosis without pericardial or myocardial involvement. Acid-fast tubercle bacilli were secured in all 12 patients with tuberculous pericardial effusion and in 20 patients with pulmonary manifestations only; the cause of constrictive pericarditis had to be determined partly

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from old records and anamnestic data. Pericardial constriction was demonstrated by right heart catheterization.

Ninety-eight healthy patients with all blood types and 10 patients with Coxsackie B-myocarditis, on whom data have been published,[10] served as control subjects.

Immunologic investigations: All studies were performed in sera stored at −25°C for up to 5 years. Indirect immunofluorescence was carried out on cryostat sections and air-dried morphologically intact cardiocytes.[10] A modification of the indirect technique[13] was performed using operatively resected myocardium from patients with congenital heart disease (blood group 0). Skeletal muscle, kidney, homologous thyroid gland, uterus and skin, heterologous (rat) liver, esophagus, and stomach were also used. After testing with polyspecific fluorescein-isothiocyanate (FITC)-labelled antiserum ($F[ab]_2$ fragments, H- and L-chain specific: fluorescence/protein (F/P) molar ratio 2.5 ± 1.5, total protein content 23 to 25 mg/ml, dilution 1:10, Behring) immunoglobulin class specificity was analyzed with monospecific FITC-labeled antisera ($F[ab]_2$ fragments, H- and L-chain specific, Behring) and anti-C_3 antiserum (Behring). The antimyolemmal subtype of antisarcolemmal antibodies was determined in isolated cardiocytes, which were deprived of their basement membrane by treatment with collagenase[10]: Vital cardiocytes were allowed to settle in a cylindrical chamber, air-dried and fixed with acetone for 20 minutes. Indirect immunofluorescence was carried out as described earlier.

Antibodies were classified either as muscle-specific or non–tissue-specific. Subtypes of the muscle-specific antibodies included those directed against the sarcolemmal (ASA) and myolemmal (AMLA) membrane, against muscle fibrils (AFA) and the contractile proteins myosin and actin, or against interfibrillary substance (IFA) (Fig. 1). Tissue-nonspecific antibodies found in this study were antinuclear antibodies (ANA), smooth muscle antibodies (SMA), antimitochondrial antibodies (AMA), and antibodies directed against capillaries and the endothelium of small vessels (AEA). A heterologous renal tubular immunofluorescent pattern associated with a positive antisarcolemmal and antiendothelial reaction was attributed to heterophil antibodies and was therefore excluded. Antibodies against double-stranded desoxyribonucleic acid were tested radioimmunologically (Amersham).

Assays of antibody-mediated target cell lysis (AMC): Vital cardiocytes were isolated according to Powell and Twist[14] and enriched to more than 90% vital cells by continuous silica sol gradient centrifugation.[10] Vitality was judged according to shape (cylindrical = vital and spherical = nonvital) and the exclusion of trypan blue.

Assays:

1. Two hundred μl of cardiocytes in a modified Krebs-Ringer solution (NaCl 120.5, NaH/CO_3 13.1, KCl 2.6, KH_2PO_4 1.18, $MgSO_4$ 1.18, CaCl 0.55, and glucose 11.1 mmol/liter and 0.1% [weight/volume] Pentax Fraction V bovine serum albumin type F [Sigma]) in a concentration of 5×10^4 cells/ml were placed in the wells of microtiter plates (Falcon multiwell 3008). Additions were 50 μl decomplemented serum and 50 μl of human complement (fresh normal serum). After shaking for 10 seconds, 200 to 400 cells/well were counted and then incubated at 37°C (5% CO_2). The percentage of vital cells was assessed again after 12 and 24 hours. The assay was done in duplicate for each serum with a 5% limit of tolerance in counting between both samples. For each duplicate the half-life of the cardiocytes present in the patient's serum (t_{50i}) was compared with the half-life of cardiocytes in an identical representative control serum (t_{50c}). The cardiocyte index of antibody mediated cytolysis (CI_{AMC}) was calculated using the following formula: $CI_{AMC} = t_{50i}/t_{50c}$. In normal subjects (n = 80) $CI_{AMC} = 0.92 \pm 0.07$ (mean ± standard deviation). Effective cytolysis was assumed when CI_{AMC} was less than 0.8.

2. Rat hepatocytes were used in control assays. They were obtained by isolation procedures already described.[14] Assays of hepatocytolysis were carried out with hepatocytes resuspended in minimal essential medium (MEM) containing Earl's Spinner BSS with Glutamin and 20 mmol HEPES (pH 7.2) in concentrations of 5×10^4 cells/ml. The index of hepatocytolysis (HI_{AMC}) of 12 control sera was 0.95 ± 0.12 (mean ± standard deviation).

Statistical analysis: Results are given as means ± standard deviation (SD). After testing the homogeneity of variances with the Fisher test, a standard *t* test was used to evaluate the significance of differences among groups of patients. For paired samples the corresponding *t* test was used. All tests were two-tailed. In the case of inhomogeneity of variances a Welch test was employed.

The significance of correlations was tested by regression analysis. The regression was tested for linearity by variance analysis. All other statistical comparisons were performed with the chi-square test using Yates' correction factor.

Results

Clinical data: The incidence of both exudative tuberculous and constrictive pericarditis due to former tuberculous pericarditis was 2 patients/year. In the 5 years of this investigation, 12 of 97 patients with tuberculosis had pericardial effusions. However, the 12.4%

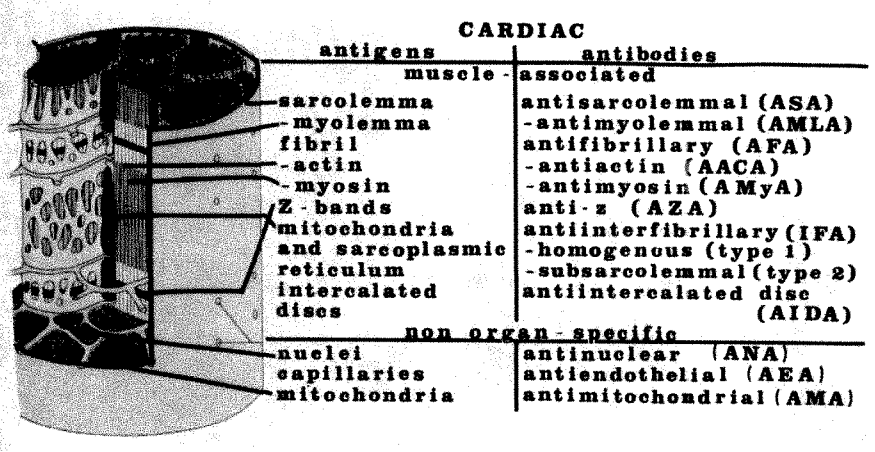

FIGURE 1. Cardiac antigens and their respective cardiac autoantibodies.

frequency of tuberculous pericarditis exceeds the natural incidence of pericarditis in patients with tuberculosis substantially because patients with pericardial symptoms were transferred from other hospitals. Thus, in 8% of all patients with pericarditis (n = 49) admitted to our hospital in 1976 to 1981—patients with postpericardiotomy and postinfarction syndromes were excluded—tuberculosis was the underlying cause. Thirteen patients had pericarditis of viral origin (10 Coxsackie B, 2 influenza, and 1 mumps), 10 had uremia, and the cause in the remaining patients was unresolved. Patients with constrictive pericarditis were seen either before pericardectomy (3 patients), because of cardiac insufficiency or coronary heart disease (4 patients) and/or because of diabetes mellitus (3 patients).

TABLE I Anamnestic and Clinical Data in Exudative and Constrictive Tuberculous Pericarditis

	Number Positive	
	Exudative Pericarditis (n = 12)	Constrictive Pericarditis (n = 10)
Nonspecific symptoms		
Fatigue	12	9
Sweats	12	2*
Increased sedimentation rate >12 in 1st hour	12	2*
PPD cutaneous reaction positive	12	10
Temperature >38°C	11	1†
Myalgia	3	0
Ascites	2	2
Cardiac symptoms		
Dyspnea	12	8
Precordial pain	11	2
Arrhythmia	3	1
Additional manifestations of tuberculosis		
Lung	12	10
Lymphadenitis	10	7
Exudative pleuritis	5	9
Myocarditis	4	Unknown
Urogenital system	1	1
Risk factors		
Diabetes mellitus	3	3
Silicosis	1	1
Alcoholism	2	1
Cirrhosis of the liver	2	2
Treatment with steroids or immunosuppressive agents	1	0
Sex		
Male	10	8
Female	2	2
Electrocardiogram		
Low voltage	6	5
ST-T segment elevation	5	0‡
Negative T wave	4	4
Ischemic ST-T segment Displacement	3	2§
Tachycardia	11	4
Ectopic beats	2	1
Atrial flutter	1	3
Heart block	1	2
Echocardiography/X-ray film		
Pericardial effusion	8	0‖
Effusion >500 ml	6	6¶
Pericardial calcification	1	10#
Cardiomegaly (heart-thoracic ratio >0.5)	3	0

Statistical evaluation: * $\chi^2 = 15.09$, 2p <0.001; † $\chi^2 = 14.67$, 2p <0.001; ‡ $\chi^2 = 5.39$, 2p <0.05; § $\chi^2 = 6.71$, 2p <0.05; ‖ $\chi^2 = 10.48$, 2p <0.01; ¶ $\chi^2 = 6.88$, 2p <0.01; # $\chi^2 = 18.33$, 2p <0.001.
PPD = purified protein derivative.

Male patients prevailed in both groups (Table I). Three of 12 patients with tuberculous pericarditis and 2 of 10 with constrictive pericarditis were of foreign (Mediterranean) nationality.

Diabetes mellitus and alcoholism were the most important risk factors of tuberculosis (Table I). Frequent nonspecific symptoms were fatigue, fever, and sweats in exudative pericarditis; leading cardiac symptoms included dyspnea and precordial pain (Table I). Pulmonary manifestations of tuberculosis were observed regularly followed by mediastinal lymphadenitis and exudative pleuritis. A diagnosis of probable myocarditis was made in 4 patients by electrocardiography, echocardiography, or both. Electrocardiographic features observed regularly were tachycardia and ST-T segment alterations showing either elevation, T-wave depression or negative T waves in exudative pericarditis. Low voltage in limb leads was seen in only 50% of patients, and atrial flutter was found in 3 of 10 patients with constrictive pericarditis (Table II). Pericardial effusion of greater than 500 ml was seen in 6 patients, necessitating pericardial puncture in all and consecutive operative treatment in 4 patients due to impending cardiac tamponade. Pericardectomy in patients with constrictive pericarditis had to be performed in only 3 cases.

Autoantibodies in exudative tuberculous pericarditis: The presence of antisarcolemmal antibodies and their muscle-specific subtype of antimyolemmal antibodies (Fig. 2) in all patients was the characteristic immunologic feature of acute tuberculous pericarditis and of viral pericarditis (Table II). ASA was associated with non–organ-specific antiendothelial and antibasement membrane antibodies in 42% of patients. Because the cardiac sarcolemma is composed of at least 3 different layers—the basement membrane, reticulin, and the myolemma itself—and many more antigenic moieties, antisarcolemmal and antiendothelial antibodies were most likely directed against antigenic sites shared between connective tissue and the sarcolemmal basement membrane.

Muscle-specific antimyolemmal antibodies, however, which were observed in all patients, could only be distinguished on vital or acetone-fixed cardiocytes, which have been deprived of their basement membrane by treatment with collagenase (Fig. 2).

The frequency of antisarcolemmal and antimyolemmal antibodies was significantly higher in patients with exudative tuberculous pericarditis than in those with pulmonary tuberculosis ($\chi^2 = 22.08 > 10.83 = \chi^2_{0.001}$; 2p <0.001), constrictive pericarditis ($\chi^2 = 13.0 < 10.83 = \chi^2_{0.001}$; 2p <0.001), and normal subjects (n = 98; 2 only positive for antimyolemmal antibodies; $\chi^2 = 92.36$; 2p <0.00001). Antimyolemmal antibodies were of the IgG class in 10 of 12 patients and of the IgM class in only 4 patients. They fixed complement in 5 patients' sera.

Antifibrillary antibodies were secreted in 75% of patients with exudative pericarditis, this occurring significantly more often than in constrictive pericarditis ($\chi^2 = 9.3$; 2p <0.01) and in control subjects ($\chi^2 = 47.03$; 2p <0.00001). Antimyosin antibodies (Fig. 3) prevailed in 8 of the 9 patients. They are the serologic marker

TABLE II Autoantibodies in Exudative Tuberculous Pericarditis and Chronic Constrictive Pericarditis (1976 to 1981)

Antibody Type	Percent Positive			
	Tuberculous Pericarditis (n = 12)	Chronic Constrictive Pericarditis (n = 10)	Tuberculosis Without Pericarditis (n = 20)	Viral Pericarditis Coxsackie B (n = 10)
Muscle-specific				
Antisarcolemmal (ASA)	100	10	10	100
Antimyolemmal (AMLA)	100	10	0	90
Antifibrillary (AFA)	75	10	10	10
Antimyosin (AMyA)	67	10	10	10
Antiactin (AAcA)	8	0	0	0
Anti-interfibrillary (IFA)	25	10	10	20
Non–organic-specific				
Antiendothelial (AEA)	42	20	10	80
Antismooth muscle (SMA)	8	0	0	10
Antinuclear (ANA)	33	10	0	0
Antimitochondrial (AMA)	33	10	10	10

Healthy normal subjects (n = 98): all antibodies less than 8%.

discriminating best between tuberculous (positive) and viral pericarditis (negative), since in the latter cases they were missed frequently.

Autoantibodies in constrictive pericarditis, pulmonary tuberculosis, and control subjects: Frequency of muscle-specific and non–organ-specific autoantibodies in patients with chronic constrictive pericarditis and in those with pulmonary tuberculosis without pericarditis did not significantly exceed the frequency in normal subjects (n = 98) (Table II).

Demonstration of antibody-mediated cytolysis: Cytolytic serum activity against vital heterologous cardiocytes was closely related to the presence of antimyolemmal antibodies in titres greater than 1:20. Only 1 patient's serum, which did not demonstrate antimyolemmal antibodies, induced cytolysis nonspecifically; in all other cases cytolytic activity increased proportionally with the reciprocal AMLA titer. Whereas 1 of 8 sera with AMLA titers of 1:20 induced cytolysis in the presence of complement, 2 of 3 with a titer of 1:40 and 3 of 4 with a titer of 1:80 were cytolytic (Fig. 4). By linear regression analysis between the reciprocal AMLA titers and the index of antibody-mediated cardiocytolysis, a fair correlation between both variables was established ($y = -0.0045x + 1.02$; $r = 0.62$).

In 4 of 5 patients with pericarditis, whose sera were cytolytic, myocardial involvement was made likely by electrocardiographic criteria (ST-T segment displacement, atrial flutter, and heart block) and by cardiomegaly. In these patients additional heart disease such as coronary and valvular heart disease could be excluded.

The following additional experimental data also support an antibody-mediated process and make unspecific cardiocytolysis in vitro unlikely:

1. Only antimyolemmal antibodies bind to vital cardiocytes as observed by indirect immunofluorescence (n = 10). Sera containing antifibrillary antibodies only

FIGURE 2. Demonstration of antimyolemmal antibodies by indirect immunofluorescence using acetone-fixed rat cardiocytes. A linear staining is observed along the glycocalix or myolemma.

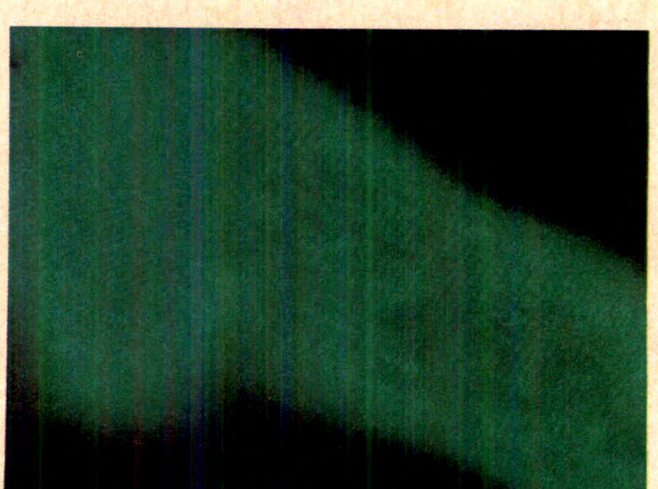

FIGURE 3. Demonstration of antifibrillary antibodies of the antimyosin type. The thick filaments are stained by this patient's serum with tuberculous perimyocarditis. The antigen used for indirect immunofluorescence was acetone-fixed rat cardiocytes.

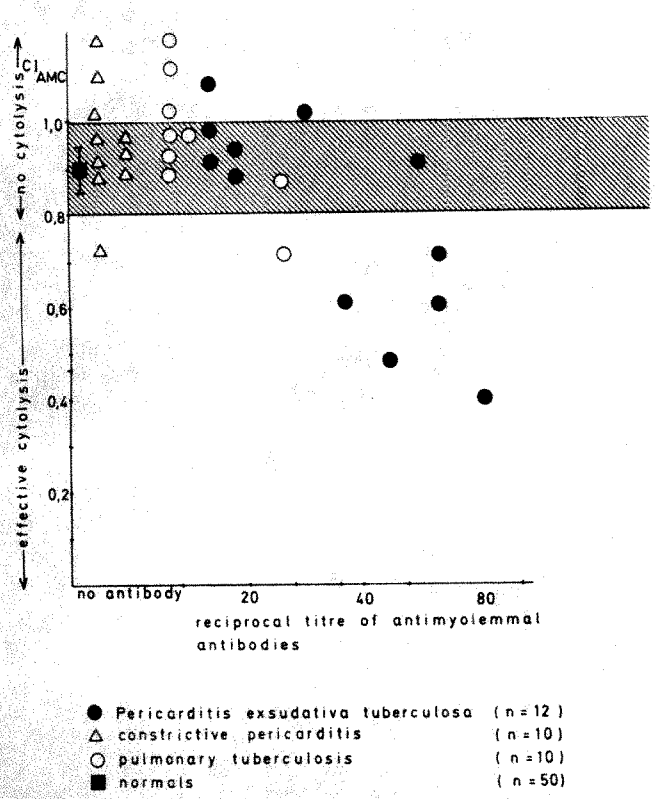

FIGURE 4. Correlation between reciprocal titres of antimyolemmal antibodies and antibody mediated cytolysis (AMC). The degree of AMC is expressed by the cardiocyte index of AMC (CI_{AMC}). Effective cytolysis can be expected if CI_{AMC} is lower than 0.8. It could be demonstrated that sera containing antimyolemmal antibodies in high titres induced cytolysis of vital adult cardiocytes in patients with exudative tuberculous pericarditis. In contrast, no cytolysis was observed in AMLA-negative sera of patients with constrictive pericarditis, in patients with pulmonary tuberculosis, and in normal subjects.

gave no intracellular staining when incubated with *vital* myocytes.

2. Antimyolemmal antibodies did not stain the membrane of other target cells such as rat hepatocytes (n = 10).

3. When sera, which contained antimyolemmal antibodies, were absorbed with a pellet of vital cardiocytes (n = 8), they became AMLA-negative. Before absorption, strong cytolytic activity with an index of cytolysis (CI_{AMC}) of 0.58 ± 0.06 was demonstrated. After absorption the CI_{AMC} had normalized by reaching 0.89 ± 0.07. Absorption of the sera with equal amounts of rat hepatocytes did not significantly alter the immunofluorescent pattern of cardiocytes nor the cytolytic serum activity. Sera containing antimyolemmal antibodies in titres of 1:40 and 1:80 were not cytolytic to different target cells such as rat hepatocytes (n = 5; HI_{AMC} = 0.96 ± 0.15, as compared with 0.95 ± 0.12 in 12 normal controls).

4. In the absence of complement no cytolytic activity of AMLA-positive sera against cardiocytes was observed. This indicates that complement had to be bound to the antibody for the cytolytic reaction (n = 5).

5. Immune complexes of aggregated IgG (A-IgG) in concentrations of 10 to 250 μg/ml did not adhere to the membrane of vital and acetone-fixed cardiocytes (n = 5), nor did they induce cytolysis of cardiocytes (CI_{AMC} = 0.97 ± 0.04 for 50 μg A-IgG/ml, and 0.94 ± 0.08 for 250 μg A-IgG/ml).

Discussion

Clinical data: In our area tuberculosis remained the most frequent single infective pericarditic pathogen, followed by viral perimyocarditis of the Coxsackie B type.[12,15] Bacterial pericarditis other than from tuberculosis was found only once in a patient with staphylococcal perimyocarditis. Pericarditis after cardiac surgery was much more common in our patients[16–18] than in any single viral or bacterial pericardial disease. However, it is controversial whether the postpericardiotomy syndrome is caused by autoimmune reactions alone[18,19] or occurs in the presence of an infection, which may be viral.[20]

The clinical manifestations of tuberculous pericarditis in our patients does not substantially differ from the findings in previous studies[21] with respect to male preponderance, nonspecific and cardioselective symptoms, risk factors of tuberculosis, clinical manifestations, and electrocardiographic and laboratory findings. In addition to pericardial involvement, clinical data indicated that myocardial involvement was likely in 33% of our patients. With the exception of pericarditis after radiation in Hodgkin's disease,[22] repeated pericardial puncture or pericardiocentesis, or both, had to be performed most often in patients with tuberculous pericarditis.

Diagnostic and pathogenetic significance of antimyocardial antibodies: Muscle- and non–organ-specific autoantibodies have been described in several cardiac diseases such as rheumatic carditis,[23] viral perimyocarditis,[11,12,15] infective endocarditis,[24,25] postpericardiotomy,[16,17,19,20] and postinfarction syndromes.[26–28] These antibodies have not been reported in patients with tuberculous pericarditis. Non–organ-specific autoantibodies, however, were described in patients with mycobacterial infection without pericardial involvement, such as leprosy.[29] In tuberculosis, autoantibodies were reported only in animal models such as rabbits infected with acid-fast bacilli: Non–organ-specific antibodies were directed against a variety of antigens present in liver, spleen, kidneys, heart, lung, and lymph nodes.[30]

Our studies clearly demonstrate the presence of antisarcolemmal antibodies and their muscle-specific subtype, the antimyolemmal antibodies, in exudative tuberculous pericarditis. Together with antifibrillary antibodies, they indicate perimyocardial manifestation in tuberculosis because they were not found in patients with pulmonary tuberculosis. As compared with patients with viral pericarditis, whose sera also contained antimyolemmal antibodies, the additional presence of antifibrillary antibodies was the discriminating factor adding to specificity. Both antibodies were also markers of disease activity: In constrictive pericarditis due to previous tuberculous pericarditis the incidence was only 10% and titers were low.

Antisarcolemmal antibodies can be directed not only against the myolemma but also against the non–organ-specific moieties of the sarcolemmal basement membrane. A cross-reaction of antisarcolemmal antibodies with moieties of connective tissue of the pericardial sac and the basement membrane of the myocardial cell is therefore very likely. However, their muscle-specific subtype, the antimyolemmal antibodies, were found in all patients with tuberculous pericarditis.

Whereas antisarcolemmal antibodies are heterogeneous, antimyolemmal antibodies appear cardiospecific. In this study heterophil antibodies[31] and isoantibodies against blood group substances[32] were excluded by the use of both homologous (human blood group 0) and heterologous myocardium (rat/bovine) and the elimination of antibody patterns typical for heterophil antibodies. The muscle-specific antimyolemmal antibody pattern was identified by the use of cardiac muscle cells deprived of reticulin and collagenous parts of the basement membrane[33] after treatment with collagenase.[10,11]

We could also exclude nonspecific absorption of immune complexes through their Fc-receptors by cardiac antigens from negative tests with aggregated IgG (unpublished data).

The presence of complement-fixing muscle-specific antimyolemmal antibodies of the IgG type most likely indicates myocardial involvement in tuberculous pericarditis. All 4 patients with clinical evidence of myocarditis in tuberculous pericarditis demonstrated antibody-mediated cytolysis induced by complement and antimyolemmal antibodies in titers of more than 1:40. Further studies have to be performed to determine whether antimyolemmal antibodies in tuberculous pericarditis are cross-reacting to antigenic moieties of the pathogenic agent involved, as has been demonstrated in rheumatic fever[23,34,35] and viral perimyocarditis.[11] In previous studies performed in our laboratory it could be established that subgroups of antimyolemmal antibodies and cytolytic activity against vital cardiocytes can be absorbed completely with the respective viral antigen (in Coxsackie B, influenza, and mumps perimyocarditis).[11]

Moreover, our data suggest that cytolysis of vital cardiocytes is induced by complement-fixing antimyolemmal antibodies. Cardiocytolysis was present only in sera containing antimyolemmal antibodies. Their titers correlated with the cytolytic serum activity.[11] An additional effect of cytotoxic serum factors[36,37] which do not necessarily belong to the immunoglobulins cannot be ruled out completely. Cardiocytolysis was effective only in the presence of antibody and complement since it was not observed when cardiocytes were incubated with decomplemented sera only.[11]

Our studies favor the possibility that antibody-mediated cytolysis in vitro represents a model of the secondary immune process that could be operative in vivo. With the exception of antimyolemmal antibodies all other antimyocardial or non–organ-specific antibodies do not affect vital cardiac cells in vitro and vivo. They are most likely "innocent bystanders."

The occurrence of antimuscle antibodies directed against the myolemma and fibrils has been temporarily related to tuberculous pericarditis. Because there was clinical evidence of additional myocardial involvement in many patients, antimyolemmal and antifibrillary antibodies are indicators of myocardial inflammation as well. Moreover, cardiocytolysis mediated by AMLA-positive sera in the presence of complement in vitro indicates that a secondary immune process may be operative in vivo. Cytolytic antimyolemmal antibodies may be both temporarily and causally related to perimyocarditis in tuberculosis.

In several studies[5,7] the complex immunopathogenesis of tuberculosis has primarily been based on cell-mediated immune reactivity. Humoral antibodies were inversely proportional to the variables of cell-mediated immunity.[6] Our investigations demonstrate that in tuberculous pericarditis, B-cell effector mechanisms such as antimyolemmal antibodies are operative regularly. It may be concluded from these data that tuberculous pericarditis occurs predominantly in patients with a partial defect of cell-mediated immunity. Further studies are underway to investigate cell-mediated immunity, the relevance of host resistance, and its possible genetic control in patients with tuberculosis and perimyocardial inflammation.

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Constrictive Pericarditis: New Aspects

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The current status of constrictive pericarditis is reviewed with regard to its etiology, physical signs, electrocardiographic findings, and hemodynamic features. Angiographic aspects are also presented. The role and limitations of M-mode echocardiography in this disease are emphasized. The value of other noninvasive studies such as measurement of systolic time intervals, myocardial scanning, and high-speed echocardiography is described. Emphasis is placed on the invasive and noninvasive methods that may be useful in separating restrictive cardiomyopathy from constrictive pericarditis. Methods of treatment, indications for pericardial resection, and the current operative results are commented on briefly.

Constrictive pericarditis is an uncommon disease but an important one. It represents a potentially curable cause of circulatory dysfunction manifested by persistent dyspnea, fatigue, and elevated systemic venous pressure. During the past few years, much new information has appeared concerning the etiology and physiology of constrictive pericarditis. The application of new methods has materially advanced our ability to understand and recognize the physiologic disturbances associated with this disease. This important information concerning etiology, the mechanism of physical signs, hemodynamic features, effects of fluid challenge, systolic time intervals, echocardiograms, and studies with ventriculograms and echocardiograms recorded at fast speed is reviewed herein.

Etiology

During the past few decades, the etiologic background of pericardial disease in general, and of constrictive pericarditis in particular, has changed. Tuberculosis was formerly considered the most common recognizable cause of chronic constrictive pericarditis,[1,2] but acute nonspecific pericarditis may be more common in later series.[3,4] In the series of Wychulis et al.,[4] idiopathic pericarditis was the most common antecedent, but in most cases the cause was unknown. In effusive-constrictive pericarditis, neoplasm, radiation therapy, rheumatoid arthritis, and idiopathic pericarditis are common causes.[5] The long survival of patients with end-stage renal disease has allowed patients with uremic pericarditis to develop constrictive pericarditis in some instances.[6–9] Patients with metastatic neoplasm, including lymphomas, may develop constrictive pericarditis, either because of neoplastic involvement of the pericardium, or because of radiation therapy directed toward the mediastinum. Immunosuppressive therapy has permitted longer survival of patients with connective tissue disease, some of whom have pericardial disease, including constrictive pericarditis. Rheumatoid arthritis has emerged as a not uncommon cause of pericardial constriction.[10–16] Rheumatic fever is still regarded as a rare cause of constrictive pericarditis. Purulent pericarditis may be a complication of connective tissue disease in a patient with impaired host defense mechanisms. Most pericardial infections, including viral infections,[17–19] have the possibility of constrictive pericarditis as a late complication. Intrapericardial bleeding after trauma[20] or diagnostic procedures or pacemaker insertion[21] may be followed by constrictive pericarditis.

Of particular recent interest is the constrictive pericarditis associated with mulibrey nanism. Constrictive pericarditis was found in 8 of 26 patients with this disease; one was reported from the U.S.A. and 3 from Canada.[22] The others reported were from Finland, with the exception of 1 from Egypt. Constrictive pericarditis after radiation therapy directed toward the mediastinum may be delayed for years after such therapy. A recent report[23] of 9 cases of radiation-induced pericardial fibrosis described a delay of 53 to 124 months between the original treatment and the later diagnosis of pericardial disease. In 3 reported cases[24,25] there was a possible relationship of constrictive pericarditis to methysergide therapy. Two reports[26,27] of constrictive pericarditis after Dressler's postmyocardial infarction syndrome have appeared in the literature. The association between congenital atrial septal defect and constrictive pericarditis is recognized but difficult to explain.[3,28–30]

Constrictive pericarditis after cardiac operations is uncommon but is now being recognized. Three cases were reported[31] in 1979 after coronary artery bypass grafting. Three other cases after cardiac valve replace-

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ment were reported from New York in 1979[32]; we have had experience with 3 such cases. Marsa[33] reports that 19 instances have now been described. The largest series is that reported by Kutcher et al.[34] from Emory University. They found 11 instances of constrictive pericarditis after about 5,000 cardiac operations; the incidence was 0.21%. Evidence of cardiac constriction was usually present within 3 to 6 months after operation, and in some within a few weeks. A possible relationship between constrictive pericarditis and the use of povidone-iodine pericardial irrigating solution has been raised.

Physical Signs

Cervical veins: A consistent feature of the disease is persistent elevation of systemic venous pressure even after treatment with diuretics, digitalis, sodium restriction, and rest. The frequent presence of Kussmaul's sign in constrictive pericarditis and its absence in cardiac tamponade has been emphasized by Spodick[35] and others.

Paradoxical pulse: A paradoxical arterial pulse (inspiratory decline of systolic blood pressure of 10 mm Hg or greater) is present in nearly every patient with cardiac tamponade associated with pericardial effusion unless there is left ventricular dysfunction, atrial septal defect, or aortic incompetence. This sign is absent in most patients with constrictive pericarditis and indeed was found in only 1 of our last 13 cases, and was of borderline degree in that 1. On the other hand, Wise and Conti[36] found pulsus paradoxus in 10 of 22 cases of constrictive pericarditis, and Wychulis et al.[4] in 40 of 137.

Pericardial knock: Another important physical sign is the pericardial knock sound. This diastolic sound associated with constrictive pericarditis tends to occur earlier in diastole than the normal third heart sound or the S_3 gallop sound associated with myocardial dysfunction. The knock sound interval from the aortic component of the second heart sound is usually 0.06 to 0.10 second rather than 0.12 to 0.16 second as found with third heart sounds and S_3 gallop sounds. The genesis of the pericardial knock sound was studied by Tyberg et al.,[37] who found that the timing of the pericardial knock sound corresponded to that of a sudden and premature plateau of the diastolic left ventricular volume curve, occurring on the average at the time of completion of 85% of the ventricular filling in early diastole. This plateau was missing in 2 patients with constrictive pericarditis who had no pericardial knock sound. In those 2, the rate of ventricular filling was faster than normal in the first 20% of diastole. This study supported the view that the sudden cessation of rapid ventricular filling generates the pericardial knock of constrictive pericarditis. Nicholson et al.[35] reported the knock to be increased by squatting and phenylephrine infusion and eliminated by nitroglycerin therapy.

Electrocardiography

The usual electrocardiogram in constrictive pericarditis shows nonspecific S-T and T abnormalities, and low voltage QRS without patterns of bundle branch block or ventricular hypertrophy. In one study, 6 of over 100 patients had right ventricular hypertrophy,[39] a prevalence of 5%. We[40] reported on a 13 year old patient who had pericardial fibrosis with constriction in the atrioventricular groove leading to a variety of mitral stenosis whose electrocardiogram had evidence of left atrial and right ventricular enlargement in lead V_1—thus stimulating the electrocardiogram of mitral stenosis. Five cases were described with subpulmonary stenosis due to a constricting band of pericardium; right ventricular hypertrophy was reported in 1.[40a]

Hemodynamic Features

Several hemodynamic features of the disease deserve comment. These include angiographic features, the radiologic appearance of the right atrial angiocardiogram, the comparison of ventricular and atrial pressure pulses in constrictive pericarditis and in cardiac tamponade, systolic time intervals, and the results of fluid challenge in patients with occult constrictive pericarditis.

Angiography: Motion of the free wall of the right ventricle showed diastolic restriction in both constrictive pericarditis and in restrictive cardiomyopathy; normal motion of the crista supraventricularis was seen in constrictive pericarditis but not in restrictive cardiomyopathy.[41]

Right atrial angiocardiogram: In constrictive pericarditis the 3 characteristics of the right atrial angiocardiogram are increased thickness of the right atrial wall plus pericardium beyond the normal value of 3 to 5 mm, straightening of the right heart border without the normal lateral convexity, and poor pulsations of the right atrial wall. Although usually present, a typical angiocardiogram may be absent and was not seen in 3 of our last 13 patients with constrictive pericarditis.

Pressure pulse in right atrium and the ventricles: It is well recognized that the characteristic deep *x* and *y* descents in the right atrial pressure pulse and the square root sign in the right and left ventricular pressure pulses are present in nearly every case of constrictive pericarditis and are not found in the typical case of cardiac tamponade. In patients with effusive-constrictive pericarditis, the *x* and *y* descents may not be prominent at first, but with removal of the fluid the hemodynamic effects of the underlying constrictive process are unveiled; then the *x* and *y* descents may be prominent and the square root sign appears.

Systolic time intervals: Nine cases of constrictive pericarditis were studied.[42] Left ventricular ejection time (LVET) was shortest in patients with congestive heart failure, averaging 359.9 ms; it averaged 392.3 ms in constrictive pericarditis and 403.3 ms in normal subjects. Mean PEP (preejection period)/LVET was 0.48 in patients with congestive heart failure, 0.31 in those with constrictive pericarditis, and 0.28 in normal subjects.

Results of fluid challenge: Bush et al.[43] in 1977 reported the effects of a volume challenge produced by infusion of 1 liter of normal saline solution during a period of 6 minutes in patients with occult constrictive

pericardial disease, in those with cardiomyopathy, and in a small group of normal subjects. In normal subjects, mean right atrial and pulmonary wedge pressure did not rise more than 3 mm Hg with the fluid challenge. In those with occult constrictive pericardial disease, postinfusion levels of right atrial and pulmonary wedge pressure were comparable to each other and there was diastolic equilibration of right atrial and pulmonary wedge pressure which had been absent before. All patients with occult constrictive pericarditis developed an *x-y* right atrial pressure contour during volume expansion, whereas this did not occur in normal subjects. In patients with myocardial disease, volume expansion did not lead to equilibration of pulmonary wedge and right atrial pressure, and only a few exhibited *x-y* contour of the pressure pulse in the right atrium.

Echocardiography

There is no single diagnostic or specific echocardiographic pattern in constrictive pericarditis. Gibson et al.[44] reported abnormal ventricular septal motion in 8 of 10 patients with constrictive pericarditis. Diminished systolic motion was followed by unusual posterior motion in diastole. In a review of our 12 patients who had echocardiograms, Peter Engel in our laboratory found abnormal systolic septal motion in 5, abnormal diastolic septal motion in 4, thickened pericardium in 6 of 11, and left ventricular posterior wall diastolic flattening in 8 of 11.

Schnittger et al.[45] found evidence of pericardial thickening in their cases of constrictive or constrictive-effusive pericarditis. Six of 14 patients with constrictive pericarditis had abnormal ventricular septal motion, and 9 of 14 had diastolic flattening of left ventricular posterior wall motion.

Voelkel et al.[46] reported that diastolic motion of left ventricular posterior endocardium was less than 1 mm in 11 of 12 patients with constrictive pericarditis; it was 1.5 to 4.0 mm in 10 normal subjects. Horowitz et al.[47] reported systolic septal thickening of 18 to 45% in 11 patients with constrictive pericarditis, and 9 to 11% in 6 patients with restrictive cardiomyopathy. Mintz et al.[48] reported a lack of respiratory variation in inferior vena caval echocardiographic dimension in patients with constrictive pericarditis or right ventricular dysfunction. In another study[49] computer tomography was of value in recognizing constrictive pericarditis or pericardial effusion in some patients whose echocardiograms were not satisfactory for this purpose.

Distinction From Restrictive Cardiomyopathy

Considerable interest has focused on the problem of separating restrictive cardiomyopathy, especially that due to amyloid disease, from constrictive pericarditis. The patient with restrictive cardiomyopathy may have a paradoxical arterial pulse and persistent elevation of systemic venous pressure with prominent *x* and *y* descents, and may have normal ventricular dimensions on the echocardiogram. Studies of filling patterns of the left ventricle by 2 means, (1) angiography and (2) high speed echocardiography, may aid in the differentiation of constrictive cardiomyopathy and constrictive pericarditis. Tyberg et al.[50] studied by angiography 7 normal subjects, 7 patients with constrictive pericarditis, and 4 with cardiac amyloid disease. The critical separation among the 3 groups was achieved at 50% of diastole. In patients with constrictive pericarditis 85% of left ventricular filling was achieved by the completion of 50% of diastole; this value separated the cardiac filling pattern in constrictive pericarditis from that in normal subjects (65% of filling of the left ventricle by completion of 50% of diastole) and that in 4 patients with amyloid disease (50% of filling of the left ventricle by completion of 50% of diastole). Meyer et al.[51] studied the rate of left ventricular filling in these 3 conditions by high speed echocardiography and found that the rate of left ventricular filling was more rapid in constrictive pericarditis than in restrictive cardiomyopathy. The interval from minimal left ventricular dimension (end-systole) to maximum left ventricular filling was 0.05 ± 0.01 second in constrictive pericarditis and 0.11 ± 0.03 second in restrictive cardiomyopathy.

Wizenberg et al.[52,53] studied 10 patients with cardiac amyloidosis, each of whom had symmetrical left ventricular posterior wall and septal hypertrophy on echocardiography. Six of 7 had an increased PEP/LVET ratio (0.46 to 0.83). Each exhibited decreased systolic thickening of the septum and posterior wall. Each of the 10 patients had a diffuse myocardial uptake of technetium pyrophosphate (4+ in 9 and 3+ in 1).

Tei et al.,[54] in a preliminary communication, reported an echocardiographic study of 12 patients with restrictive cardiomyopathy and 13 with constrictive pericarditis. An abnormal atrial systolic notch of interventricular septal motion was found in 7 of 8 patients with constrictive pericarditis who had sinus rhythm and in none of the 12 with restrictive cardiomyopathy.

Treatment

The treatment for chronic constrictive pericarditis is generally considered to be pericardiectomy, for which operation the current mortality rate is 4 to 6%.[4,55,56] However, in some series[56] the death rate was 20%. Culliford et al.[55] presented an argument for resection of the pericardium from all surfaces of the heart and intrapericardial vessels. The administration of digitalis, sodium restriction, and diuretics may be helpful in some instances,[56] especially when there is impairment of myocardial function. When the operation is adequately carried out, two thirds or more of the patients show major long-term improvement.[4,55] In some instances immediate pericardiectomy is not essential. In patients who have mild or no functional impairment, operation may be deferred since the process ordinarily progresses very slowly. When operation is delayed for years, one must consider the possibility of a more difficult operation later with a higher risk of mortality, as well as increasing damage to the myocardium.

The place of operative treatment in the management of occult constrictive pericarditis[57,58] *remains unsettled.* Since these patients, who have little or no resting hemodynamic impairment, may usually be ex-

pected to do well for an extended period of time, there is a question as to whether or not an operation of more than minimal risk should be undertaken to relieve a condition that is not life-threatening.[59]

Other groups of patients with constrictive pericarditis may require extensive evaluation before a decision is made concerning pericardiectomy. Among these are elderly patients with minimal impairment or extensive pericardial calcification, those with other diseases limiting life expectancy or quality of life, and those with a high likelihood of myocardial damage, such as patients with radiation-induced pericarditis.

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Echocardiographic Study of Right Ventricular Wall Motion in Cardiac Tamponade

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Twenty-one patients had M-mode echocardiographic recordings during cardiac tamponade. Seventeen of 21 had posterior motion of right ventricular endocardium at 0.05 second or longer after opening of the mitral valve. Sixteen of 17 patients with a large pericardial effusion without cardiac tamponade had posterior right ventricular wall motion that ceased at 0.05 second or less after opening of the mitral valve. The finding of early diastolic posterior motion of the right ventricular wall may signify diastolic collapse of the right ventricle and aids the echocardiographic identification of cardiac tamponade.

Echocardiography is the most sensitive tool for the detection of pericardial effusion. As little as 15 ml of pericardial fluid can be detected with this technique.[1] Large effusions are also easily identified. Determination of the hemodynamic consequences of pericardial effusion by echocardiography has proved more challenging. Preliminary reports[2,3] suggest that persistence of systolic posterior motion of the right ventricular wall into diastole may serve as an echocardiographic marker of cardiac tamponade. The purpose of the present study was to critically examine the usefulness of this sign in a large series of patients with cardiac tamponade examined with echocardiography.

Methods

Patients: The clinical records of all patients with the diagnosis of pericardial effusion with cardiac tamponade seen at our institution between 1972 and 1980 were reviewed. Cardiac tamponade was defined as inspiratory decline greater than 10 mm Hg in systolic arterial blood pressure and elevated systemic venous pressure in the presence of pericardial effusion. If a drainage procedure was performed (21 patients), then the elevated venous pressure and pulsus paradoxus improved or resolved.

Fifty-five such patients were identified, of whom 24 were examined with M-mode echocardiography and formed the study group. A control group of M-mode echocardiograms consisted of 17 unselected studies from patients with a large pericardial effusion without clinical evidence of tamponade.

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Echocardiography: The studies were performed with either a Smith-Kline Ekoline 20 or an Irex System II instrument using standard techniques. Strip chart recordings were made at either 50 or 100 mm/s paper speed.

Motion of the right ventricular endocardium was analyzed using both the electrocardiogram and mitral valve motion for reference. The point in time when the right ventricular posterior motion ceased was termed the X point (Fig. 1). Note was made of the relation of the X point to the electrocardiographic T and P waves. For quantitation of this relation, the interval between the preceding R wave and the X point was divided by the preceding R-R interval to form the ratio R-X/R-R.

Particular attention was paid to the interval between mitral valve opening and the X point (MVO-X). If the mitral valve opening preceded the X point, a positive value is obtained for MVO-X. If the X point occurred before mitral valve opening, the MVO-X interval is negative. If no anterior echo-free space was apparent, the study was not included in subsequent analysis. The minimal right ventricular diastolic dimension was measured as the distance between right ventricular endocardium and the right side of interventricular septum at the X point.

Analysis of data: The echocardiographic measurements were made independently by 2 observers unaware of the clinical status of the patients. Major discrepancies were resolved by consensus. The measurements reported represent the average of the 2 independent measurements in each case. The sensitivity of a test for a condition is defined as the probability that it will be positive in patients with the condition; the specificity is defined as the probability that the test will be negative in patients without the condition. The predictive value of a positive test is defined as the probability that the condition is in fact present, given a positive test result.

Results

Clinical diagnosis: Forty-one patients were studied with M-mode echocardiography. Twenty-four had clinical or hemodynamic evidence, or both, of cardiac

tamponade, whereas 17 had a large pericardial effusion without evidence clinically or hemodynamically of cardiac tamponade. Of the 24 patients with tamponade, 12 had malignant pericardial effusion, 3 had an effusion that was considered viral or idiopathic in origin, 2 had tuberculous pericarditis, 3 had uremic pericarditis, and 1 each had bacterial pericarditis, systemic lupus erythematosus, postpericardiotomy syndrome, and aortic dissection.

MVO-X interval: One patient in the group with effusion without tamponade and 3 in the group with tamponade had echocardiograms in which the X point could not be identified due to the absence of anterior pericardial effusion; these studies were excluded from subsequent analysis. The mean value (± standard error of the mean) for the mitral valve opening-X point (MVO-X) interval was −0.04 ± 0.01 second in the group without tamponade and +0.09 ± 0.02 second in the tamponade group. Seventeen of 21 patients with tamponade had an MVO-X interval of +0.05 second or greater, whereas 15 of 16 patients with a large effusion without evidence of tamponade had an interval measuring +0.05 second or less (Fig. 2). Thus, with +0.05 second as the cutoff point, a prolonged MVO-X interval had a sensitivity of 81%, a specificity of 94%, and a predictive value of 89% as an echocardiographic sign of tamponade in this group of patients. Measurement of the MVO-X interval was reproducible, as evidenced by a mean difference between the 2 observers of 0.01 second; a Z value of 2.44 was obtained when the Wilcoxon rank test was applied to the paired observations.

In the 18 patients in whom the volume of pericardial effusion was measured at the time of pericardiocentesis or surgery, a significant correlation was found between the size of the effusion and the MVO-X interval (Fig. 3). Of note is the fact that of the 4 patients with tamponade with an MVO-X interval less than +0.05 second, 3 had an effusion of less than 500 ml.

R-X/R-R interval: The echocardiographic X point occurred after inscription of the electrocardiographic T wave in almost every case. Measurement of the R-X/R-R ratio did not improve separation between the

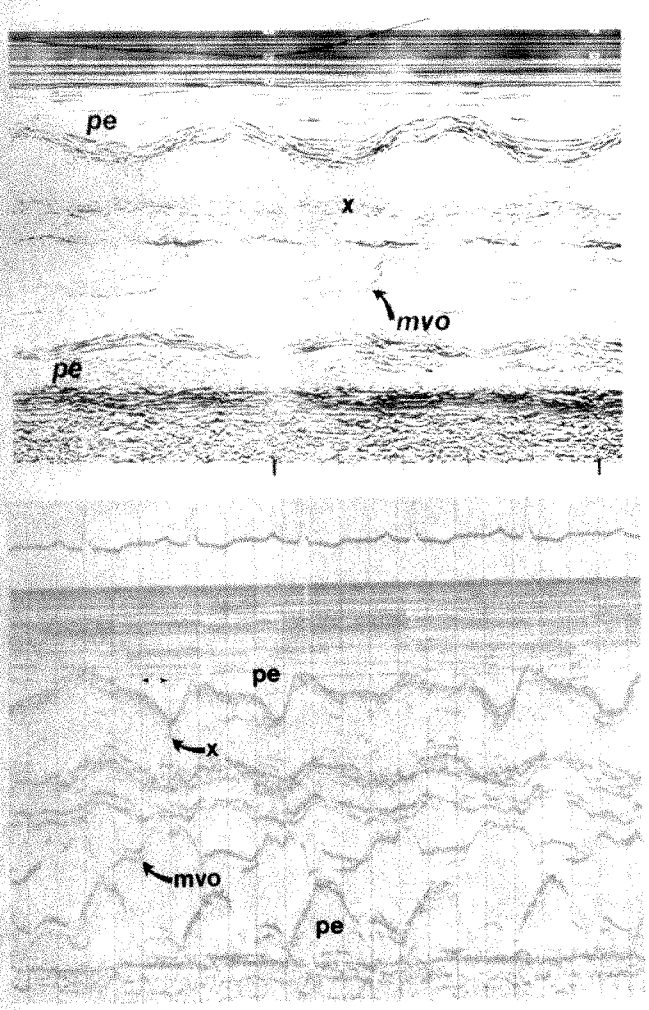

FIGURE 1. Top, simultaneous M-mode recording of right ventricular wall and mitral valve motion from a patient with a large pericardial effusion (pe) without tamponade, demonstrating the time of cessation of posterior motion (x) of right ventricular wall and the time of mitral valve opening (mvo). Paper speed is 100 mm/s. **Bottom,** similar recording from a patient with pericardial effusion and cardiac tamponade. Note the diastolic posterior movement of the right ventricular free wall (prolonged MVO-X interval). Paper speed = 50 mm/s. Time lines (**arrowheads**) = 0.2 second.

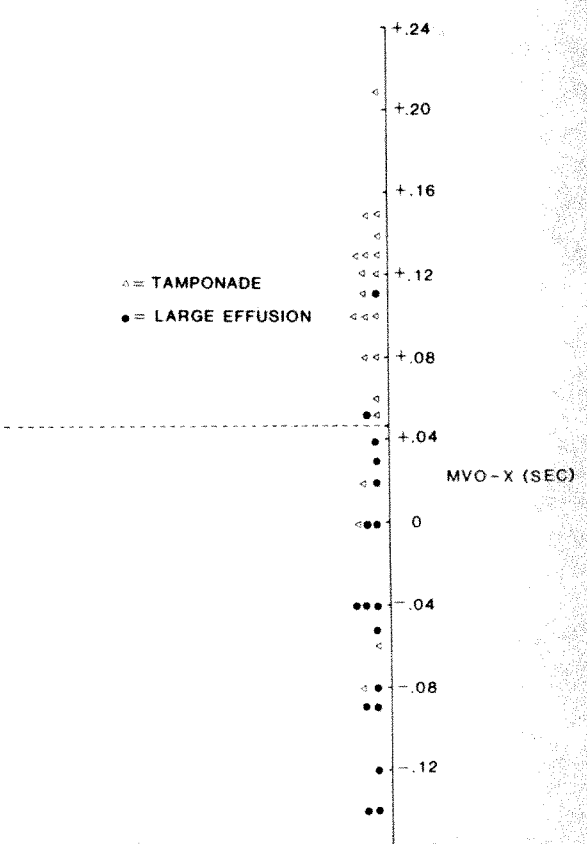

FIGURE 2. Comparison of measurement of MVO-X interval in patients with (**triangles**) and those without (**circles**) cardiac tamponade.

patients with and those without tamponade, as there was considerable overlap between the 2 groups (Fig. 4).

Right ventricular diastolic dimension: No value allowed separation between the groups with and those without tamponade when minimal diastolic dimension of the right ventricle was measured (Fig. 5), although the mean value of the group with tamponade (1.1 cm) was smaller than that of the group without tamponade (1.5 cm).

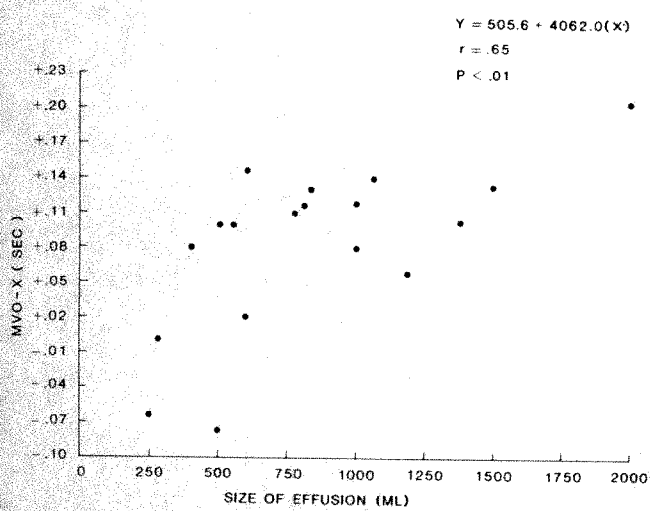

FIGURE 3. Graphic representation of the relation between the volume of pericardial effusion and the MVO-X interval in 18 patients with cardiac tamponade.

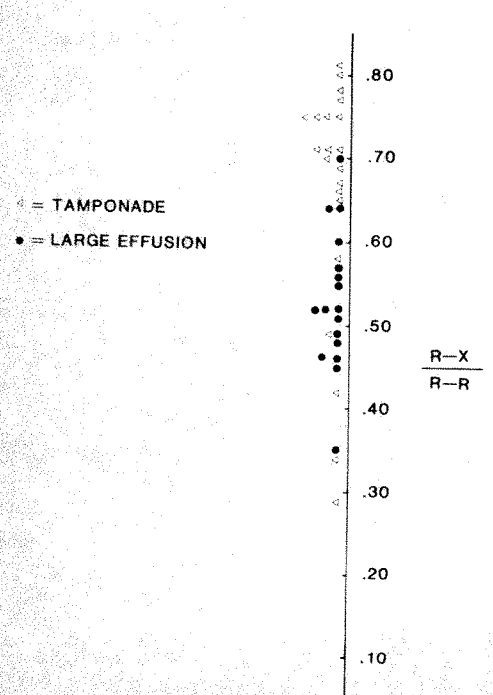

FIGURE 4. Comparison of measurement of R-X/R-R ratio in patients with (**triangles**) and those without (**circles**) cardiac tamponade.

Relief of tamponade: In the 19 patients studied with echocardiography after relief of tamponade, diastolic posterior motion of the right ventricular endocardium was no longer present.

Discussion

Previously described echocardiographic signs of pericardial tamponade: Since the initial description of the identification of pericardial fluid by echocardiography,[4] considerable study has been devoted to the echocardiographic detection of pericardial effusion and its consequences. A noninvasive marker of cardiac tamponade would be of major importance to the clinician, as this complication of pericardial effusion is life-threatening and treatable.

Previous investigators noted a number of findings on echocardiography in patients with cardiac tamponade. Reciprocal respiratory variation in ventricular dimensions was reported,[5,6] but was found to be nonspecific for tamponade because this sign is present in other conditions characterized by greater than normal inspiratory decline in arterial blood pressure.[7,8] An early systolic "notch" on the time-motion recording of the right ventricular wall was described in some patients with cardiac tamponade,[9] but this was not confirmed in a larger series.[10] Expiratory right ventricular compression (right ventricular end-diastolic dimension less than 8 mm) was noted in some studies[11]; however, this abnormality is often noted only in retrospect, that is, after relief of tamponade.

Diastolic posterior right ventricular motion: Preliminary observations[2,3] suggest that posterior motion of the right ventricular wall continues into diastole in patients with tamponade. Martin et al.[12] previously described diastolic "invagination" of the right ventricular wall in 3 patients with a large pericardial effusion studied by 2-dimensional echocardi-

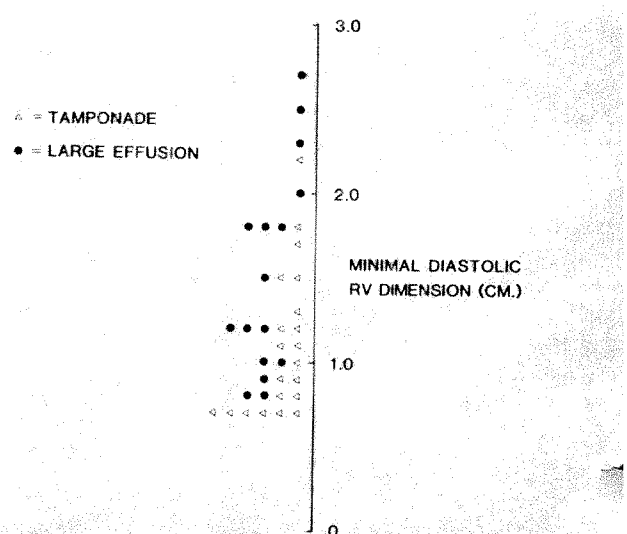

FIGURE 5. Comparison of measurement of minimal right ventricular (RV) diastolic dimension in patients with (**triangles**) and those without (**circles**) cardiac tamponade.

ography. In the present study, we retrospectively examined the M-mode echocardiograms of a large group of patients with pericardial effusion with and without evidence of tamponade with particular emphasis on motion of the right ventricular wall. We found that diastolic posterior right ventricular motion was common in this group of patients. In order to accurately time the cessation of this posterior diastolic motion, it was compared with the motion of the simultaneously recorded mitral valve. We found that persistence of posterior motion of the right ventricular endocardium longer than 0.05 second after mitral valve opening (prolonged MVO-X interval) correlated with the presence of tamponade.

Although none of our patients was studied with 2-dimensional echocardiography, it seems likely that this abnormal motion reflects early diastolic invagination of the collapsible right ventricle. Early diastolic leftward and posterior motion of the interventricular septum has been described in patients with mitral stenosis[13] and was thought to possibly represent left ventricular filling by suction.[14] A similar process may be operative in tamponade[15] and may explain the early diastolic motion abnormality of the right ventricular wall in the present group of patients.

Factors affecting motion of the heart in pericardial effusion: Several factors have been described as affecting the motion of the heart within the pericardial sac when pericardial effusion is present. The volume of the effusion is probably a critical factor. We found a rough correlation between the size of the effusion and the timing of the right ventricular wall motion; the smallest effusions were associated with the shortest MVO-X intervals and with false-negative tests for tamponade by this measure. The size of the effusion and the rapidity of its accumulation influence intrapericardial pressure, which also affects cardiac motion in pericardial effusion. This factor as well as the viscosity of the pericardial fluid may have been operative in the false-negative results in the patient with aortic dissection in this series, who presented with shock and cardiac tamponade. Finally, adhesions may have been present between the visceral and parietal pericardium in some of the patients with more chronic conditions in our series. Such adhesions are not routinely discovered by M-mode echocardiography and may restrain cardiac motion within a larger pericardial effusion.

Clinical implications: No single test detects cardiac tamponade with complete accuracy, and the clinical diagnosis of tamponade may be difficult. Previously described echocardiographic signs of this condition may lack sensitivity and specificity. The finding of persistent diastolic posterior motion of the right ventricular wall is a useful echocardiographic sign of cardiac tamponade when an anterior pericardial effusion is present, particularly because the right ventricular wall is often the easiest cardiac structure to image with ultrasound in patients with larger pericardial effusions. The finding of right ventricular endocardial posterior motion greater than 0.05 second after mitral valve opening adds to the reliability of the echocardiographic diagnosis of cardiac tamponade.

Acknowledgment

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Two-Dimensional Echocardiographic Findings In Cardiac Trauma

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Cardiac contusion is a potentially fatal complication of blunt chest trauma. The diagnosis is obscured because cardiac contusion usually occurs in a setting of multisystem trauma. Furthermore, the electrocardiographic changes are nonspecific. Experience with 2-dimensional echocardiography in evaluating cardiac trauma has not previously been emphasized. This report examines the results of 2-dimensional echocardiographic examinations in 7 patients after significant blunt chest trauma. Generalized right ventricular dilatation was identified in 4 cases; superimposed segmental areas of right ventricular dilatation occurred in 3. Three patients had localized myocardial thinning, and segmental wall motion abnormalities occurred in 2. Additional abnormalities identified included ventricular thrombi (4 right and 1 left ventricular), fibrinous pericardial effusion (1), ruptured tricuspid chordae with flail leaflet (1), and a small aneurysm of the sinus of Valsalva (1). It is concluded that 2-dimensional echocardiography is useful for diagnosing cardiac contusion, for estimating the extent of myocardial damage, and for identifying accompanying cardiac lesions such as thrombi, pericardial effusion, and valvular disruption.

Cardiac contusion is an increasingly recognized entity in patients with nonpenetrating chest injury.[1] The yearly incidence of cardiac trauma in the United States is estimated at 900,000 cases.[2] Although the cardiac lesion may be clinically silent and may be masked by damage to other organs, it can also result in serious or fatal complications.[1-13] In patients with multiple injuries, determination of the severity and extent of associated cardiac trauma may affect management, particularly if operation under general anesthesia is contemplated.

Unfortunately, the diagnosis of cardiac trauma, particularly cardiac contusion, is imprecise and may be confounded by the presence of associated injuries, hypoxia, shock, and metabolic abnormalities. The clinical diagnosis has been based primarily on serial electrocardiographic changes, but these are often nonspecific.[1-5,7,9-12] More recently, creatine kinase isoenzyme determinations[14,15] and radionuclide cardiac scanning[9,13,16-19] have shown promise. Experience with 2-dimensional echocardiography in the evaluation of chest trauma victims has not previously been emphasized. The 7 patients in this report illustrate the value of 2-dimensional echocardiography in assessing cardiac trauma and its sequelae. Two-dimensional echocardiography was helpful in demonstrating wall motion abnormalities, myocardial hematoma, intracavitary thrombus, pericardial effusion, and valvular dysfunction. We believe the direct observations afforded by 2-dimensional echocardiography reflect the nature and extent of cardiac injury and are helpful in the management of these patients.

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Methods

Echocardiography: Two-dimensional echocardiographic examinations were performed with a wide angle, phased-array sector scanner (Varian 3000 or 3400) with a 32 element, 2.25 MHz transducer. When the patient was too ill for transport, examination was performed at the bedside.

Our technique for 2-dimensional examination in acquiring multiple tomographic cardiac sections was previously described.[20] Techniques for imaging and assessing abnormal right and left ventricular segments were also previously described.[21,22] We judged a segment to be abnormal if it was thin, dyskinetic, akinetic, or poorly contractile according to visual

TABLE I Clinical and Laboratory Data in 7 Patients

	Patient						
	1	2	3	4	5	6	7
Age (yr) & sex	27M	20M	41M	22F	50M	16F	21M
Type of accident; associated injuries	Single car, driver; struck chest on steering wheel; soft tissue injuries	Single car, passenger; rib fractures and lacerations	Two-car, driver; struck chest on steering wheel; abrasion over sternum plus multiple lacerations	Single car, driver; pulmonary contusion and fractures of pelvis, scapula, and lumbar spine	Fell 20 feet from roof and struck chest, face, left arm, and leg; multiple fractures of arm and ribs and abrasions	Single car, passenger; pelvic fracture, corneal abrasions, and multiple lacerations	Single car, passenger; dental fracture, closed head injury, and fracture of left femur
Chest symptoms	Sharp, nonpleuritic chest pain, relieved on sitting	Chest pain (in area of rib fractures)	Chest pain, increased with deep breath or movement of left arm	None	None	None	Chest pain consistent with pericarditis; progressive dyspnea on exertion
Cardiovascular examination	Initial: normal; 24 h: loud S_4, triphasic friction rub	Normal	S_4 gallop	Rales in left chest; copious amounts of bright red blood on suctioning	Normal	Normal	New murmurs of aortic insufficiency and tricuspid insufficiency
Electrocardiogram	Day 1: S-T elevation, II, III, aVF, and V_4-V_6 S-T changes normalized by day 10; decreased voltage developed	Day 1: T inversion V_1 and V_2; Day 3: T inversion V_1-V_5; Day 4: frequent VPCs; Day 6: resolving T changes	Day 2: mild sinus bradycardia; serially unchanged	Day 1: T inversion II, III, aVF; T flattened V_5 and V_6; Day 2: normal	Sinus bradycardia (46/min), unchanged from 2 yr earlier; early repolarization II, III, aVF; serially unchanged	Day 4: Slight S-T elevation II, III, aVF; serially unchanged	Incomplete RBBB, vertical QRS axis
Chest X-ray	Day 1: generous heart size and mediastinum, fluid in right chest; increasing cardiomegaly through day 10	Right and left 2nd rib fractures, small right pneumothorax, infiltrate right midlung	Normal	Bilateral pulmonary contusions	Left rib fractures, diaphragmatic hernia	Normal	Cardiomegaly with unusual left heart border
Peak enzymes*	930 MB = 5%	810 MB = 4%	410 MB = 0%	729 MB = 4%	253 MB = 0%	282 MB = 7%	. . .
Catheterization and angiography	Negative arch aortogram	None	None	None	None	None	Severe tricuspid insufficiency, mild to moderate aortic insufficiency, trivial pulmonary insufficiency, right sinus of Valsalva aneurysm, cardiac index = 1.8 liters/min/m^2
Results of initial echocardiograms	Day 2: RV dilatation, RV free wall thinning and decreased wall motion, small pericardial effusion; day 12: moderately large pericardial effusion with fibrous bands, RV thrombus	Day 7: Moderately dilated RV, lateral RV free-wall bulge, huge apical thrombus of RV	Day 3: RV thrombus	Day 5: normal RV, inferoapical LV thrombus, thinning of LV underlying thrombus	Day 2: Enlarged RV, RA, and IVC, thin and hyperrefractile RV free wall, dilated RV apex, RV thrombus	Day 5: RV free-wall akinesia, dilated RV apex	At 11 mo: ruptured anterior leaflet of tricuspid valve, severe tricuspid regurgitation,† dilated RV and RA, paradoxic septal motion, sinus of Valsalva aneurysm (right coronary cusp), possible localized dissection (aortic root)
Hospital stay	18 days: worrisome pericardial effusion	15 days: therapy of VPCs plus anticoagulant for RV thrombus	5 days	13 days: shoulder and pubic fractures	8 days: arm fracture	11 days: pubic fracture	Not known

* Creatine kinase, units/liter.
† With peripheral vein injection of indocyanine green dye.
IVC = inferior vena cava; LV = left ventricle; MB isoenzyme = myocardial fraction (value for Patient 1 given after intramuscular injection of analgesic); RA = right atrium; RBBB = right bundle branch block; RV = right ventricle; VPCs = ventricular premature complexes.

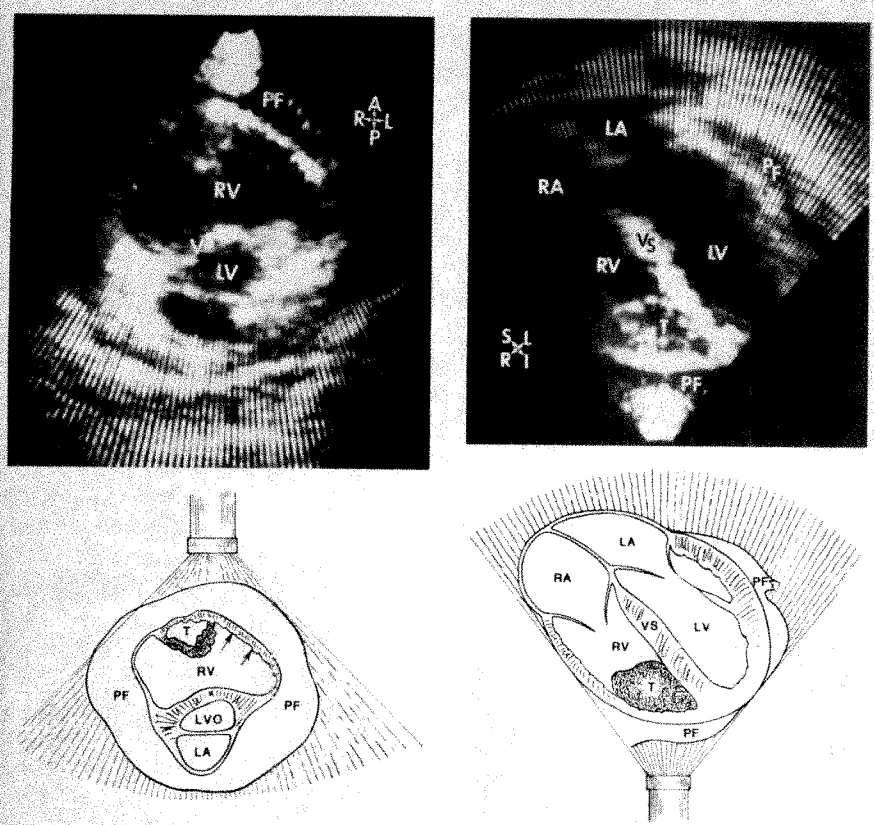

FIGURE 1. Case 1. **Left,** right ventricular contusion. Parasternal short-axis view. The right ventricle (RV) is dilated and the free wall is thinned (**arrows**). In real time the free wall was hypokinetic. Underlying the right ventricular free wall is a mural thrombus (T). Moderate-sized pericardial fluid (PF) accumulation is present. The anterior mitral leaflet separates the normal-sized left ventricular outflow tract (LVO) and the left atrium (LA). **Right,** right ventricular thrombus, 4-chamber view (precordial). The right ventricular thrombus is more clearly visualized in this view. The pericardial fluid is again demonstrated. The left ventricle (LV) is normal. A = anterior; I = inferior; L = left; P = posterior; R = right; RA = right atrium; S = superior; VS = ventricular septum.

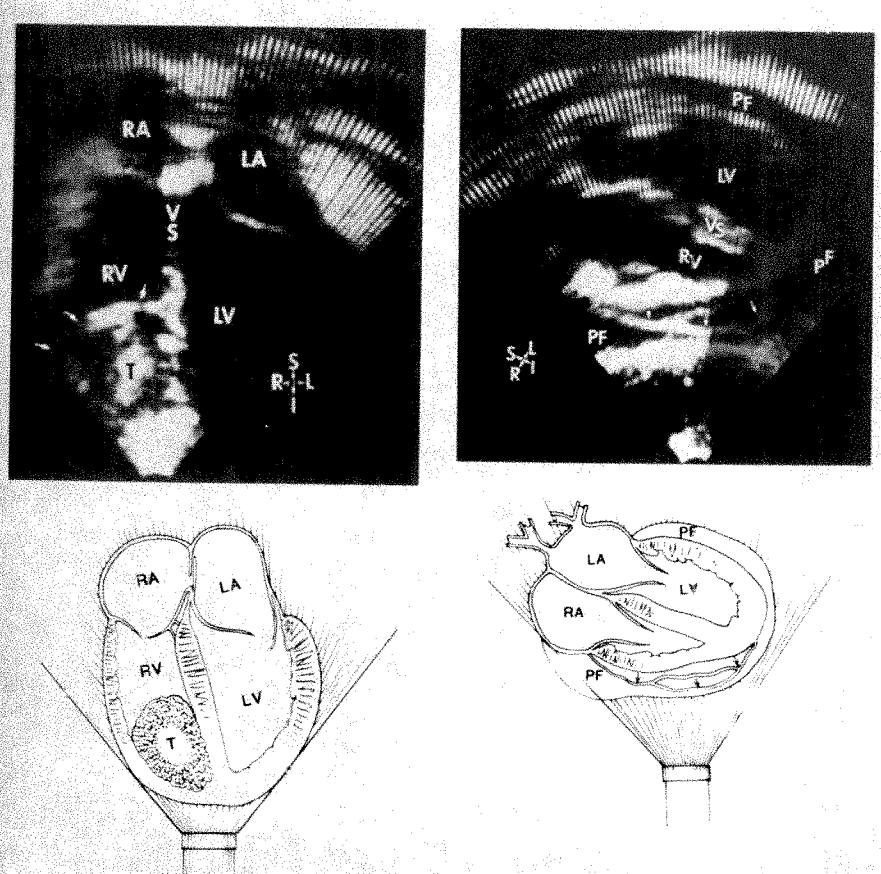

FIGURE 2, left. Case 2. Large right ventricular thrombus. In this apical 4-chamber view, the apex of the right ventricle (RV) is occupied by a large thrombus (T). This thrombus was identified on multiple views and is clearly distinct from the usual right ventricular trabeculations. The left ventricle (LV) is normal. **Arrows** indicate the proximal border of the thrombus. Abbreviations as in Figure 1.

FIGURE 3, right. Case 1. Pericardial effusion with strands. Subcostal 4-chamber view shows that the right ventricle (RV) and left ventricle (LV) are surrounded by a large collection of pericardial fluid (PF). Presumed fibrin strands are visible within the fluid-filled pericardial sac (**arrows**). A right ventricular thrombus was present (see Fig. 1). Abbreviations as in Figure 1.

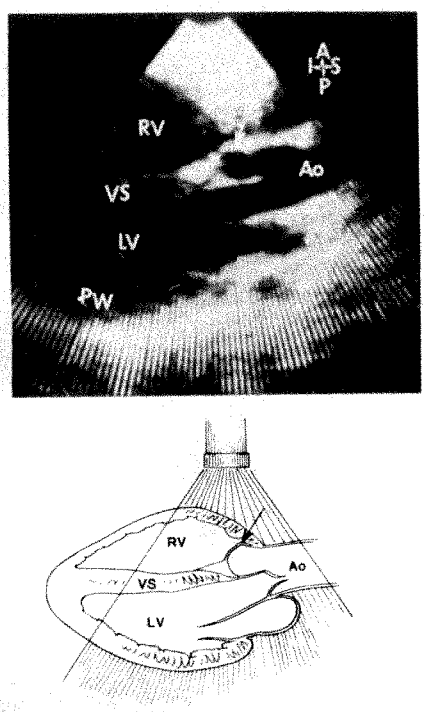

FIGURE 4. Case 7. Aneurysm of the sinus of Valsalva. In a parasternal long-axis view, there is an aneurysm, 1.5 by 1.0 cm, of the right sinus of Valsalva (**arrow**) associated with a new murmur of aortic regurgitation. The right ventricle (RV) appeared normal in this view. Ao = aorta; PW = posterior wall of left ventricle; other abbreviations as in Figure 1.

assessment. Thrombus was diagnosed when a rounded density, contiguous with a ventricular wall, was seen on multiple views.[23] Particular care was taken to distinguish such masses from the right ventricular moderator band and trabeculations. Examinations were recorded on an 0.75-inch videotape for storage and review. Illustrations for this report were obtained by photographing stop-action images from a video screen with a 35 mm camera.

Patient data: Patients' charts were reviewed with respect to the nature of their chest trauma, presenting signs and symptoms, and results of standard examinations, including chest roentgenography, electrocardiography, and cardiac enzyme determinations. Particular attention was paid to the associated cardiac complications and therapeutic interventions.

Injuries in all 7 patients resulted from deceleration accidents. Clinical details are provided in Table I. In 6 patients the initial 2-dimensional echocardiogram was obtained 2 to 7 days after trauma, and follow-up 2-dimensional examinations were performed 1 week to 3 months later. The 7th patient was referred to our institution 11 months after an automobile accident, which resulted in significant disability as a result of tricuspid valve insufficiency.

Results

Clinical findings: Four of the 7 patients had significant chest injuries including rib fracture, chest abrasion, and pulmonary contusion in conjunction with cardiac contusion (Table I). Two of the 3 remaining patients had severe associated trauma at sites distant from the chest. The initial cardiac examination gave abnormal results in only 2 patients: 1 (Case 1) with a pericardial rub and 1 (Case 7) with new murmurs of aortic and tricuspid regurgitation.

TABLE II Summary of 2-Dimensional Echocardiographic Findings

Findings	Patients (n)
Generalized right ventricular dilatation	4
Localized right ventricular dilatation	3
Localized myocardial thinning	3
Segmental wall motion abnormalities	2
Thrombi*	5
Pericardial effusion	1
Valvular rupture	1
Great vessel abnormalities	1

* Four were in the right ventricle; 1 was in the left ventricle.

The cardiac silhouette on the chest roentgenogram was normal in 5 patients and enlarged in 2 patients: the patient with pericardial effusion (Case 1) and the 1 with valvular insufficiency (Case 7). Electrocardiography gave abnormal results in 5 of the 7 patients. In 6 patients the total serum creatine kinase level was elevated at the initial evaluation, and the MB fraction was abnormal in 4. The peak creatine kinase value in 1 patient is unknown. In 2 patients (Cases 3 and 5) the clinical cardiac examination, electrocardiogram, chest roentgenogram, and MB fraction of creatine kinase were within normal limits, and the diagnosis of cardiac contusion was based solely on information supplied by 2-dimensional echocardiography.

Echocardiographic findings (Fig. 1 to 4): Cardiac abnormalities consistent with the diagnosis of cardiac contusion were visualized by 2-dimensional echocardiography in each of these 7 patients (Table I). Echocardiographic abnormalities were identified in the right ventricle in 6 patients and in the left ventricle in 1 (Table II). Four patients had generalized right ventricular enlargement and 3 had localized right ventricular dilatation (Fig. 1). In 3 there was localized myocardial thinning and in 2 hypokinesia of the right ventricular free wall. Intracavitary echo densities compatible with thrombi[23] were visualized in 5 patients (Fig. 1 and 2); 1 of these was in the left ventricle and the remaining 4 were in the right ventricle. The thrombi were usually located on or adjacent to a dilated or abnormally contracting segment of ventricular free wall or apex. A large fibrinous pericardial effusion was identified in 1 patient (Case 1) (Fig. 1 and 3). Echocardiography in Case 7 demonstrated rupture of the anterior tricuspid leaflet chordae, with flail leaflet and features of severe tricuspid regurgitation. Peripheral contrast echocardiography substantiated the presence of severe tricuspid incompetence. In this case an unsuspected aneurysm of the right sinus of Valsalva was also noted on 2-dimensional echocardiography (Fig. 4). Cardiac catheterization was subsequently performed to quantitate the amount of aortic regurgitation, which was found to be mild to moderate. In addition, both severe tricuspid regurgitation and a small sinus of Valsalva aneurysm were confirmed.

There were no deaths in this group of patients. One patient had significant ventricular ectopy which was treated with lidocaine followed by quinidine. Two of the 5 patients with intracavitary thrombi were treated with anticoagulants (Cases 2 and 4). There were no cases of clinically identifiable embolization.

Follow-up 2-dimensional echocardiograms were obtained in 6 of the 7 patients 7 days to 3 months after the initial study. Results of follow-up study were normal in 3 patients, including the 2 patients with intracavitary thrombi who had been treated with anticoagulants. In Case 5 the follow-up study was performed 7 days later, and the right ventricular dilatation and thrombus were unchanged. In Case 1 a follow-up study at 6 weeks showed resolution of the fibrinous pericardial effusion and shrinkage and increased echo-density of the right ventricular thrombus. Shrinkage and increased echo-density of the thrombus were also noted on the 30 day follow-up study in Case 3.

Discussion

Cardiac contusion in chest trauma: Clinically recognizable cardiac contusion occurs in 9 to 21% of patients with significant blunt chest trauma.[1,2,12,13] Cardiac contusion may be the most common unsuspected visceral injury leading to sudden death after chest trauma.[1] Life-threatening arrhythmias have been well recognized in both clinical and experimental contusions.[1–4,7,9–11,13,24] Other potentially fatal complications include conduction disturbances,[1–4,7] hemopericardium with tamponade,[1–4,7,10,11,13] cardiac rupture,[2–5,7,12,13] congestive heart failure,[2–5,10] and thromboembolic events.[2–6,10] Chronic cardiac disability resulting from valvular rupture,[2–4,9,10] ventricular-septal rupture,[2–4,7,9,11–13] ventricular aneurysm,[2–4,11,13] and constrictive pericarditis[2–4,8,10,13,25] have also been reported. Clearly, it is important to recognize complicating cardiac injury in patients with chest trauma.

Clinical diagnosis: Until recently the clinical diagnosis of cardiac contusion was based on a history of significant chest trauma accompanied by serial electrocardiographic changes.[1,2,4,7,9–12] The latter consist of the entire spectrum of changes typically seen after myocardial infarction, but often they are nonspecific.[26] There may be a delay in the evolution of electrocardiographic changes ranging from several hours to days after the chest trauma. These changes usually resolve more quickly than those associated with ischemic myocardial infarction. More recently, creatine kinase isoenzyme analysis has been used in the diagnosis of cardiac contusion.[14,15] The myocardial fraction reaches its peak 6 to 24 hours after trauma and returns to normal levels at 24 to 72 hours. Technetium pyrophosphate radionuclide (hot-spot) imaging has also been used to assess possible myocardial damage in trauma cases.[9,13,16–19] In cases of extensive soft tissue and skeletal damage associated with cardiac contusions, isotope imaging with pyrophosphate may not be sufficiently discriminating, particularly when there is right ventricular involvement and isotope activity is in close proximity to interfering uptake in the sternum.

Echocardiographic diagnosis: Coleman et al.[19] reported on the potential use of echocardiography in experimental left ventricular contusions. Their study utilized the M-mode echocardiographic technique, and they acknowledged the technical difficulty of obtaining satisfactory echocardiograms in the dog model. No consistent echocardiographic abnormalities were seen. Motro et al.[27] recently reported a single case of right ventricular contusion, with aneurysm formation diagnosed by 2-dimensional echocardiography and radionuclide angiography.

Our cases illustrate the potential value of 2-dimensional echocardiography in assessing cardiac contusion. As opposed to clinical, electrocardiographic, and enzyme determinations, 2-dimensional echocardiography provides a means for direct visualization of cardiac structures and chambers. Wall motion abnormalities and chamber dilatation and wall thinning permit a gross estimate of the extent of myocardial damage. Two-dimensional echocardiography allows discrimination of right from left ventricular contusion and right ventricular contusion from traumatic pericardial effusion with tamponade. The location of the right ventricle and its proximity to the anterior chest wall and sternum increase its vulnerability during chest trauma. From an electrocardiologic viewpoint, depolarization of the right ventricle is overshadowed by events in the ventricular septum and thicker-walled left ventricle.[28] Therefore, the electrocardiogram with the use of conventional leads may be an insensitive method of diagnosing right ventricular necrosis.[29,30] Attention is also drawn to the hemodynamic similarity between pericardial disease and right ventricular infarction.[31,32] This similarity applies to other conditions in which right ventricular compliance is reduced, as in patients with restrictive cardiomyopathy,[33] and it presumably also applies to right ventricular contusion. In blunt chest trauma, the echocardiographic differentiation between right ventricular contusion and pericardial effusion with cardiac restriction may be crucial to patient management. Similarly, the echocardiographic differentiation between right and left ventricular contusion appears important in making therapeutic decisions similar to those in the patient with ischemic right ventricular infarction.[31,32,34]

In the present series the finding of intraventricular filling defects, characteristic of thrombi, is of particular interest. No patient in this series had clinical evidence of systemic or pulmonary emboli. There is a single case report[6] of death secondary to pulmonary embolism 1 month after cardiac contusion, with autopsy proof of right ventricular mural thrombosis. Whether anticoagulation should be routine in cases of cardiac contusion, provided such therapy is not contraindicated by associated injuries or complications, is currently a debated and unresolved issue.[2,5,6,10,13] Whether these patients with thrombi identified by 2-dimensional echocardiography require anticoagulation cannot be answered definitively from our data. In the 2 cases in which anticoagulants were used, thrombi were not noted on follow-up examination (at 6 days and at 3 months);

in the 3 cases in which anticoagulants were not used, thrombi persisted on follow-up examinations performed 7 days to 10 weeks after the initial study.

Diagnostic implications: Accurate diagnosis of cardiac contusion is challenging because this injury usually occurs in a milieu of multisystem trauma. Two-dimensional echocardiography provides the physician with a useful, noninvasive tool for assessing trauma patients for possible cardiac contusion. It supplements the electrocardiogram and cardiac enzyme determinations in making this diagnosis by providing direct visualization of structural and motion abnormalities consistent with cardiac contusion. It also allows localization of the injury, gross estimation of the amount of myocardium involved, and documentation of complications, including mural thrombi, valvular rupture, and pericardial effusion. Data regarding the sensitivity and specificity of 2-dimensional echocardiography in the diagnosis of cardiac contusion and in predicting serious events such as tamponade, systemic or pulmonary emboli, aneurysm, cardiac wall or valve rupture, or ventricular arrhythmia await a larger prospective study.

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Assessment of Left Ventricular Relaxation in Patients With Valvular Regurgitation

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Impaired left ventricular (LV) relaxation has been demonstrated in patients with coronary heart disease and in patients with hypertrophic or congestive cardiomyopathy but not yet in those with aortic or mitral regurgitation. Indeed, in patients with valvular regurgitation the lack of isovolumic relaxation and variations in the filling rate invalidate most relaxation indexes. The aim of this study was to assess ventricular relaxation in patients with valvular insufficiency. The hemodynamic and angiographic data were analyzed during the phase of decreasing left ventricular elastance (that is, when pressure is decreasing while volume is increasing) in 57 patients (27 with valvular regurgitation, 17 normal subjects, and 13 patients with coronary heart disease). Starting from a fixed level of wall stress (40 kdyne/cm^2), we determined the incremental LV elastance (ratio $\Delta P/\Delta V$) and the changes in velocity of lengthening produced by a constant increase in LV volume (+20 ml/m^2). In aortic and mitral regurgitation, both the incremental elastance (−0.52 versus −0.95 mm Hg/ml per m^2 in normal subjects: $p < 0.001$) and the changes in velocity of lengthening (+0.76 versus +1.17 circ/s; $p < 0.05$) were abnormal. These indexes were also impaired in patients with coronary heart disease. Further, significant correlations were found in the whole group between incremental elastance and ejection fraction ($r = 0.63$), mean velocity of fiber shortening ($r = 0.62$), and end-systolic volume ($r = 0.53$), suggesting a relation between impaired incremental elastance and alterations in inotropic state or afterload, or both. This hypothesis was confirmed by the fact that patients who had a peak systolic wall stress of less than 400 kdyne/cm^2 and a normal index of inotropic state also had normal incremental elastance: in contrast, all but 1 patient with the same afterload but abnormal contractility had abnormal incremental elastance. It is concluded that abnormalities in early diastolic filling are common in patients with valvular regurgitation and are likely to be related to impaired LV relaxation.

Myocardial relaxation, the active process by which ventricular muscle returns to its initial length and tension,[1] has been extensively studied in isolated muscle[1-6] and in animal experiments.[7-11] In man, LV relaxation has been assessed using indexes such as the time course of isovolumic pressure decrease or the rate of changes in left ventricular volume or dimension during the rapid filling phase.[12-22] These approaches have provided clear evidence that LV relaxation is impaired in patients with coronary heart disease, particularly those with hypertrophic or congestive cardiomyopathy.[12-22] It has also been suggested that clinical manifestations of LV failure might partly result from such alterations in the relaxation process of the left ventricular and that several therapeutic interventions might improve this impaired process and the patient's functional symptoms.[17,18,22-24]

Despite the clinical relevance of relaxation abnormalities, it has not yet been established whether or not LV relaxation could be impaired in patients with valvular regurgitation. In patients with aortic or mitral regurgitation, the lack of isovolumic relaxation and the wide variations in filling rate invalidate classic indexes of relaxation. The aim of the present study was therefore to develop a method, based on ventricular elast-

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ance, to assess LV relaxation in the absence of isovolumic relaxation.

Methods

Study patients: Fifty-seven patients (42 men and 15 women) were included in this study. All had sinus rhythm; cardiac catheterization was performed for diagnostic purposes. Of these patients, 17 (mean age 49.6 years, range 28 to 59) who had atypical chest pain but a completely normal ventriculogram and coronary arteries were considered normal control subjects. Twenty-seven patients (mean age 44.6 years, range 22 to 69) had valve disease: 13 had mitral regurgitation, 10 had aortic regurgitation, and 4 had combined mitral and aortic regurgitation. No patient in this group had associated valvular stenosis or coronary heart disease. Mitral regurgitation resulted from mitral valve prolapse in only 2 patients and none resulted from cardiomyopathy. Thirteen other patients (mean age 48.7 years, range 37 to 61) had coronary heart disease and previous myocardial infarction.

All cardioactive drugs were discontinued at least 48 hours before the catheterization procedure, and in most cases the delay was 6 to 7 days. Informed consent was obtained from each patient, and no complication occurred as a result of this study.

Study protocol: Left heart catheterization was performed through the femoral approach with the patient in the fasting state and without premedication.[16,19] High fidelity left ventricular pressures were recorded at low (0 to 160 mm Hg) and high (0 to 40 mm Hg) gains with a 5 or 6Fr micromanometer-tip catheter (Millar Instruments). The micromanometer system was calibrated against a mercury manometer before insertion and again after withdrawal. Aortic pressure was measured through an 8Fr pigtail fluid-filled catheter connected to a Statham P23 ID strain gauge.

Left ventriculography was performed utilizing single plane 35 mm cineangiography at 50 frames/s in the right anterior oblique projection (Philips Poly-Diagnost C). The hemodynamic variables and a cine frame marker were recorded on a multichannel recording system at a paper speed of 200 mm/s (Honeywell 1858) and on magnetic tape (Honeywell 101). LV pressure during ventriculography and the time of the peak of the R wave were also sampled synchronously with frame exposure and displayed on the corresponding cine frame in digital form (Cine Data Philips).

In 8 patients with valvular disease (3 aortic, 4 mitral, and 1 combined aortic and mitral regurgitation) 20 mg of nifedipine was administered sublingually 5 minutes after the first ventriculogram was taken. A second ventriculogram was obtained 20 minutes after administration of nifedipine.

Measurements and computations: For evaluation of left ventricular function, cine films were projected to a video camera and ventricular silhouettes were outlined with a light pen on a video screen. Both premature and postpremature beats were excluded from analysis. A computer system (LVV Philips 100) derived the correction factor for X-ray magnification and calculated volumes every 20 ms applying Simpson's rule.[25]

Wall thickness at the LV equator was traced on the last diastolic frame and was computed for the subsequent frames assuming a constant LV mass.

Mid-wall circumferential stress was calculated using the formula of Sandler and Dodge[25]: Stress = $(Pb/H)\{1 - b^3/[a^2(2{\cdot}b + H)]\}$ kdyne/cm^2, where P = left ventricular pressure, H = wall thickness, a = mid-wall semimajor axis, and b = mid-wall semiminor axis.

The ejection fraction and mean velocity of fiber shortening or lengthening were calculated according to the standard formula.[26,27] Volume data were corrected for the body surface area and end-systolic or end-diastolic volumes were defined, respectively, as the smallest and largest LV volumes obtained.

Ventricular elastance: To assess LV properties during relaxation, we analyzed angiographic and hemodynamic data during the period of decreasing ventricular elastance (that is, when LV pressure was decreasing or remaining constant despite an increase in ventricular volume). Accordingly, during this period the rate of tension reduction within the ventricular walls was a primary determinant of the ventricular elastance (which was equal to the pressure/volume ratio). To evaluate ventricular elastance during this phase of diastolic filling, we computed incremental elastance (Δpressure/Δvolume) which, in contrast to the pressure/volume ratio, was not affected by absolute values of ventricular volume. In addition, to allow comparison from patient to patient despite the variations in filling rate and in ventricular size, and because ventricular elastance is continuously changing during diastole (Fig. 1), the procedure to compute incremental elastance was standardized (Fig. 2). In each patient the ratio Δpressure/Δvolume was determined starting at a common level of LV wall stress (≈40 kdyne/cm^2) and the increment in volume (ΔV) was constant approximately (20 ml/m^2). This standardized incremental left ventricular elastance (ΔP/ΔV, mm Hg/ml per m^2) was used as the first index of the diastolic properties during relaxation. The changes in velocity of fiber lengthening (Δ velocity of lengthening) attending the standard increase in ventricular volume were also computed and used as a second index of relaxation.

Index of inotropic state: Because the isovolumic and ejection phase indexes of inotropic state are of little value in patients with valve disease,[28] the slope of the linear relation between LV wall stress and volume during the late ejection was used as an index of the inotropic state. This slope was computed in 47 patients, as previously described.[29,30] Briefly, an algorithm first detected the end of systole (defined as the frame with the maximal pressure/volume ratio); starting from this frame and going backwards throughout ejection, and the stress-volume data were then fitted to linear relations using least-squares regression techniques. In each patient, the slope of the relation with the highest correlation coefficient (r, ranging from 0.95 to 0.99) and with at least 5 data points was selected to characterize the inotropic state. Previous studies in man and in dogs have shown that this index was sensitive to changes in inotropic state, but in contrast to classic ejection phase indexes it was insignificantly affected by changes in preload or afterload.[30]

Statistics: Statistical comparisons among the groups were performed with a Mann-Whitney test,[31] whereas the correlations among the different indexes of systolic and diastolic function were determined using linear least-squares regression analysis. The paired data before and after nifedipine were compared with use of a paired t test.

Results

Systolic and diastolic function under basal conditions: Table I summarizes relevant indexes of ventricular function in the 3 groups. Patients with valve disease had significant increases in LV end-diastolic pressure (17.5 ± 7.8 versus 11.0 ± 4.0 mm Hg in normal subjects; $p < 0.01$), end-diastolic volume (178 ± 48 versus 93 ± 18 ml/m^2; $p < 0.01$), and end-systolic volume (58 ± 27 versus 27 ± 9 ml/m^2; $p < 0.01$) as well as in LV

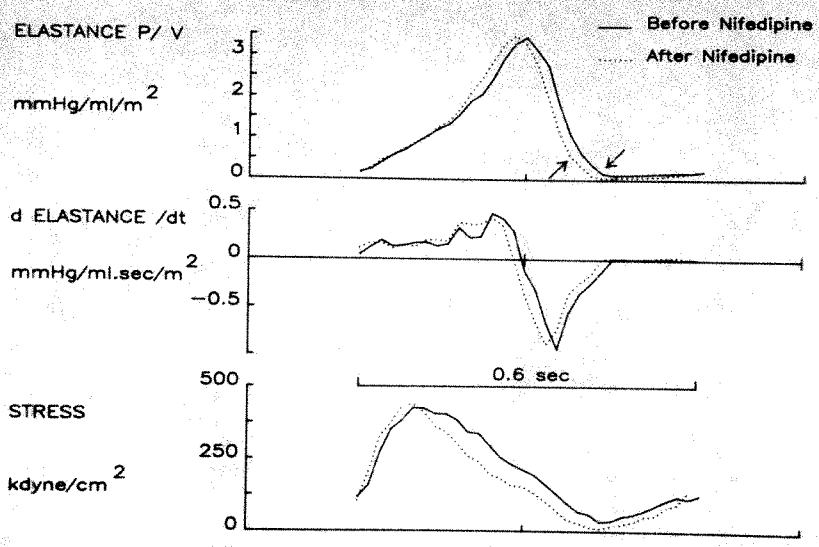

FIGURE 1. Evolution of ventricular elastance (P/V), its first derivative (d ELASTANCE/dt) and wall stress in a patient with severe aortic regurgitation, before and after administration of nifedipine. **Arrows** indicate values of ventricular elastance at a wall stress of 40 kdyne/cm^2. At this wall stress, ventricular elastance is still decreasing in both cases, as confirmed by the negative value of d Elastance/dt. After nifedipine, both mean systolic and mean diastolic wall stress were reduced and the decline in ventricular elastance occurred earlier. The end-diastolic volumes before and after nifedipine were, respectively, 132 and 138 ml/m^2, and the end-systolic volumes were 32 and 28 ml/m^2.

mass. Ejection fraction (68 ± 9%) and mean velocity of fiber shortening (1.30 ± 0.42 circ/s) were not significantly different from normal values. The slope of the late stress-volume relation, computed in 21 patients, was reduced below the lowest normal value of 3 kdyne/cm^5 per m^2 in 12 patients; this index remained within normal limits (range 3 to 9.3 kdyne/cm^5 per m^2) in 9 other patients.

The patients with coronary heart disease and previous myocardial infarction also had significant increases in end-diastolic (+ 35%; p <0.01) and end-systolic volumes (+122%; p <0.01). Ejection fraction (56 ± 9%) and mean velocity of fiber shortening (1.04 ± 0.35 circ/s) were reduced, and the peak systolic wall stress was increased by an average of 17% (p <0.05). The slope of the stress-volume relation was computed in 11 patients, only 3 of whom had a value below the lowest normal limit of 3 kdyne/cm^5 per m^2.

Table II summarizes the proposed indexes of LV relaxation during the early filling phase. Both incremental elastance (−0.52 ± 0.43 versus −0.95 ± 0.48 mm Hg/ml per m^2; p <0.01) and the changes in velocity of lengthening were significantly different from normal in patients with valvular regurgitation. Similar alter-

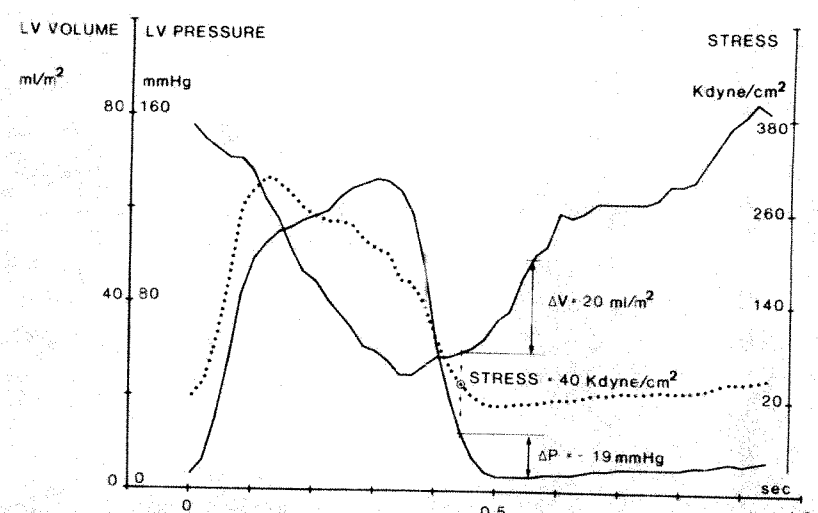

FIGURE 2. Method used to assess the LV incremental elastance ($\Delta P/\Delta V$) during ventricular relaxation. The LV pressure, volume, and wall stress of a normal subject are plotted against time. The LV pressure and volume data corresponding to a wall stress of 40 kdyne/cm^2 are first determined; then the changes in LV pressure (ΔP) attending a standard increase in volume (ΔV + 20 ml/m^2) is determined and the incremental elastance (in this case −19/20 = −0.95 mm Hg/ml per m^2) is calculated.

ations in both indexes were observed in those with coronary heart disease. LV pressure decreased in all groups during this phase, but despite identical increases in ventricular volume this pressure decrease was greater in normal subjects than in patients with heart disease. However, the range of normal values in incremental elastance was large, as was the overlap among groups (Fig. 3). The data were examined to determine the rationale for these findings.

Relations among left ventricular incremental elastance, ejection phase indexes, and peak systolic wall stress: No correlation was found between incremental elastance and age, functional class, cause of valvulopathy, grade of regurgitation, heart rate, end-diastolic pressure or volume, or left ventricular mass. However, some correlations were evident in all groups between incremental elastance and ejection fraction, mean velocity of fiber shortening, and end-systolic volume index (r = 0.63, 0.62, and 0.53, respectively; n = 57; $p < 0.001$).

Because relaxation, like ejection phase indexes, is influenced by changes in afterload, this influence was analyzed using peak systolic wall stress as an index of afterload.[32,33] This approach first indicated that the normal subjects with a peak systolic wall stress of less than 400 kdyne/cm^2 had a more negative incremental elastance than the normal subjects with a higher peak systolic wall stress (−1.07 ± 0.51 versus −0.73 ± 0.34 mm Hg/ml per m^2; $p < 0.05$). Similar trends were observed in patients with heart disease (−0.78 ± 0.40 versus −0.37 ± 0.33 mm Hg/ml per m^2; $p < 0.05$) and in patients with valve disease (−0.62 ± 0.43 versus −0.27 ± 0.32; $p < 0.025$), indicating that peak systolic wall stress had to be considered in order to correctly interpret the value of incremental elastance. However, several differences between normal subjects and patients with valvular regurgitation persisted even when the influence of the afterload was taken into account (Fig. 4). Indeed, 14 of the 27 patients with valve disease still fell outside the normal range of incremental elastance.

Relations between the slope of the late systolic stress-volume relation and LV incremental elastance: To assess the influence of inotropic state on incremental elastance, the patients were classified in 2 groups: those with a normal slope (3 to 9.3 kdyne/cm^5 per m^2) and those with a depressed slope (Fig. 5). All patients with valve disease with a low peak systolic wall stress (400 kdyne/cm^2 or less) and a normal slope fell within the normal range of incremental elastance. In

TABLE I Measurements of Left Ventricular Function

	Heart Rate (beats/min)	LVEDP (mm Hg)	EDVI (ml/m^2)	ESVI (ml/m^2)	EF (%)	Mean VCF (circ/s)	LV Mass (g/m^2)	Peak Systolic Wall Stress (kdyne/cm^2)	Slope (kdyne/cm^5 per m^2)
Normal subjects (n = 17)	73 ± 12	11.0 ± 4.0	93 ± 18	27 ± 9	72 ± 6	1.41 ± 0.28	93 ± 27	373 ± 71	5.00 ± 1.75 (n = 14)
Valvular regurgitation (n = 27)	77 ± 15	17.5 ± 7.8†	178 ±48†	58 ± 27†	68 ± 9	1.30 ± 0.42	156 ± 56†	389 ± 91	3.18 ± 1.76* (n = 21)
Coronary heart disease (n = 13)	78 ± 15	13.2 ± 7.7	126 ± 49†	60 ± 32†	56 ± 9†	1.04 ± 0.35†	116 ± 32	436 ± 85*	4.16 ± 2.75 (n = 11)

* $p < 0.05$, † $p < 0.01$.
All values are mean ± standard deviation (SD). EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; LVEDP = left ventricular end-diastolic pressure; mean VCF = mean velocity of fiber shortening; slope = slope of the linear stress-volume relation during late ejection (see Methods for explanation).

TABLE II Indexes of Ventricular Function During Early Diastolic Filling

	Starting Stress (kdyne/cm^2)	Starting Volume (ml/m^2)	Δ Volume (ml/m^2)	Δ Pressure (mm Hg)	Incremental Elastance (mm Hg/ml per m^2)	Δ Stress (kdyne/cm^2)	Δ Velocity of Lengthening (circ/s)
Normal subjects (n = 17)	40 ± 7	32 ± 11	21 ± 3	−19.5 ± 8.9	−0.95 ± 0.48	−25 ± 10	1.17 ± 1.01
Valvular regurgitation (n = 27)	39 ± 12	76 ± 33†	21 ± 4	−10.1 ± 7.2†	−0.52 ± 0.43†	−16 ± 13	0.76 ± 1.55*
Coronary heart disease (n = 13)	43 ± 11	70 ± 34†	21 ± 2	−10.3 ± 7.6†	−0.49 ± 0.39†	−19 ± 19	0.53 ± 1.12*

* $p < 0.05$, † $p < 0.01$.
All values are mean ± SD. Starting stress, starting volume, see Methods for explanation; Δ volume, Δ pressure = changes in LV volume and pressure used to calculate incremental elastance; Δ stress and Δ velocity of lengthening = changes in LV wall stress and in velocity of wall lengthening during the period when incremental elastance is computed.

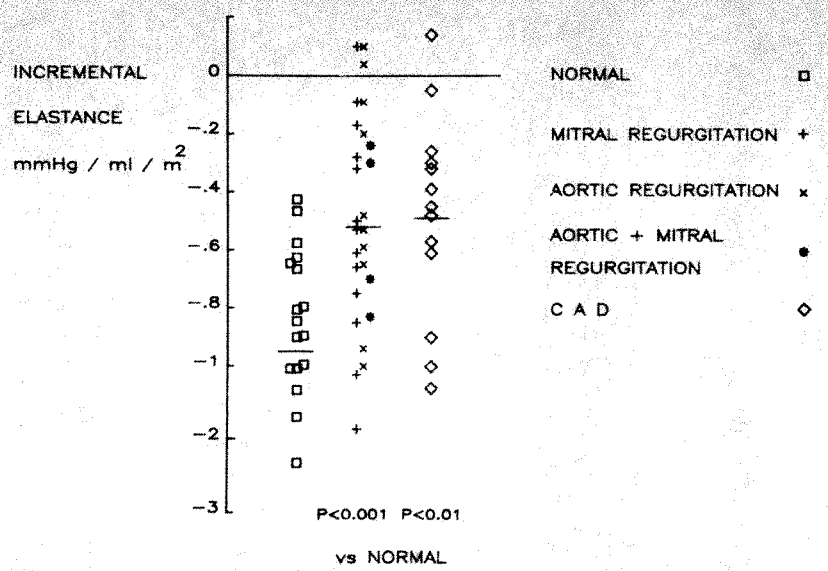

FIGURE 3. Individual values of incremental elastance in normal subjects, in patients with valvular regurgitation, and in patients with coronary heart disease (CAD). The scale of incremental elastance has been magnified between 0 and −1.

contrast, incremental elastance in all but 1 patient with valve disease with similar afterload but a depressed slope was abnormal ($p < 0.001$). When we compared patients with valve disease with a normal slope with those with an abnormal slope and impaired incremental elastance, the latter group also had significantly higher LV end-diastolic pressure (19.9 ± 8.8 versus 11.4 ± 1.9 mm Hg; $p < 0.01$), end-diastolic volume (194 ± 42 versus 141 ± 27 ml/m^2; $p < 0.01$), and end-systolic volume (62 ± 22 versus 32 ± 9 ml/m^2; $p < 0.01$). The mean velocity of fiber shortening was also reduced in this subgroup (1.23 ± 0.15 versus 1.77 ± 0.22 circ/s; $p < 0.01$) despite identical values of peak systolic wall stress. The trend was similar at a higher level of peak systolic wall stress, but the number of patients was too small for statistical comparisons (average incremental elastance in 6 normal subjects: −0.73; in 2 patients with valve disease with a normal slope: −0.47; and in 3 patients with valve disease with an abnormal slope: −0.23).

Effects of nifedipine on LV systolic and diastolic function in patients with valvular regurgitation: Table III summarizes the hemodynamic changes in-

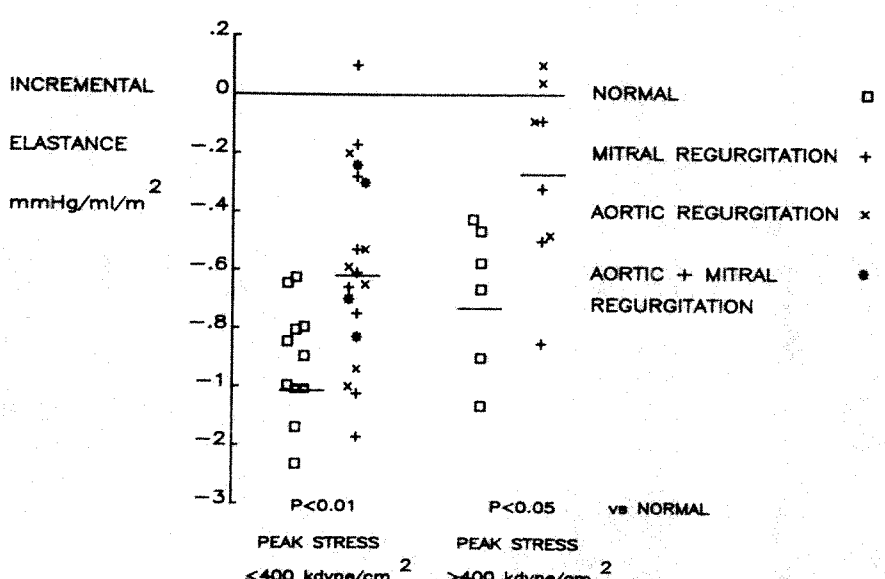

FIGURE 4. Individual values of incremental elastance in normal subjects and in patients with valvular regurgitation separated according to their value of peak systolic wall stress. Although there is a significant trend toward an increase incremental elastance with an increasing wall stress, the groups with valve disease remained significantly different from the normal group. The scale of incremental elastance has been magnified between 0 and −1.

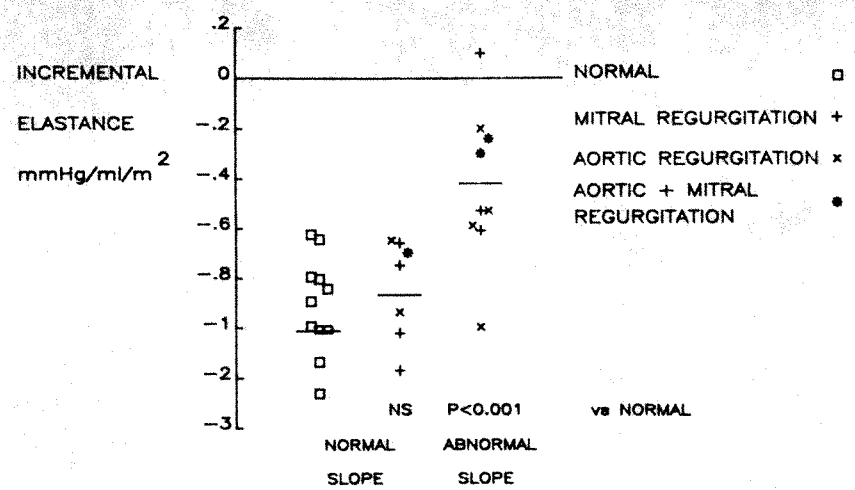

FIGURE 5. Individual values of incremental elastance in normal subjects and in patients with valve disease with similar afterload (peak systolic wall stress less than 400 kdyne/cm^2). Only the patients with valve disease and an abnormal index of inotropic state (abnormal slope: see Methods) had impaired incremental elastance. The scale of incremental elastance has been magnified between 0 and −1.

duced 20 minutes after 20 mg of nifedipine was administered sublingually to 8 patients. The late systolic slope was not significantly affected by nifedipine (−11%; difference not significant), but left ventricular systolic pressure decreased in all patients from 145 ± 27 to 125 ± 25 mm Hg ($p < 0.01$), and peak systolic wall stress was reduced in all but 1 patient. Simultaneously, small increases in ejection fraction and in mean velocity of fiber shortening and significant improvement in incremental elastance were noted. The velocity of fiber lengthening also tended to be greater, but this increase did not reach statistical significance.

Discussion

Our data indicate that an index of LV elastance determined during early diastolic filling is abnormal in many patients with valvular regurgitation or coronary heart disease. Interpretation of these observations requires consideration of several points.

Problems in assessing ventricular relaxation in valvular regurgitation: Classic indexes of LV relaxation are not valid in the absence of an isovolumic phase. Under such circumstances, indexes derived from the rate of pressure decrease such as peak−dP/dt[12] or the time constant of isovolumic pressure decrease[7–10,13,15,16,19] no longer reflect the rate of tension decrease within the myocardium but rather reflect a complex interplay between the amount of regurgitation and myocardial relaxation. Similarly, indexes based on the peak filling rate[18,20–22] or on filling fractions[20] are likely to be greatly influenced by the rapid volume overload. These problems probably explain why left ventricular relaxation has received little attention in patients with valvular regurgitation.

Under experimental conditions, when static pressure-volume or stress-strain relations are readily obtained,[34,35] it is easy to quantify the influence of relaxation during diastole even in the presence of a valve leak. However, this method is difficult to apply in patients with valve disease because hemodynamic interventions and repeated ventriculograms are required to obtain a sufficient range of static pressure-volume data. To solve these problems, it was therefore necessary to develop an index of diastolic properties, directly related to the relaxation rate and applicable both in normal patients and in patients with heart disease. It was necessary to focus the analysis on the early diastolic filling phase because during this period the relaxation rate is a pri-

TABLE III Effects of Nifedipine on Left Ventricular Systolic and Diastolic Function in Patients With Valvular Regurgitation

	Heart Rate (beats/min)	LVEDP (mm Hg)	EDVI (ml/m^2)	ESVI (ml/m^2)	EF (%)	Mean VCF (circ/s)	Peak Systolic Wall Stress (kdyne/cm^2)	Slope (kdyne/cm^5 per m^2)	Incremental Elastance (mm Hg/ml per m^2)	Δ Velocity of Lengthening (circ/s)
Control subjects (n = 8)	81 ± 20	22.6 ± 11.2	188 ± 52	56 ± 25	71 ± 6	1.38 ± 0.38	363 ± 67	2.88 ± 1.73	−0.52 ± 0.30	0.82 ± 1.17
20 minutes after nifedipine (n = 8)	88 ± 12	22.0 ± 12.2	191 ± 46	52 ± 21	74 ± 5*	1.59 ± 0.39†	320 ± 69*	2.58 ± 1.46	−0.91 ± 0.44†	1.36 ± 1.91

* $p < 0.05$, † $p < 0.01$.
All values are mean ± SD. Abbreviations as in Table I.

mary determinant of ventricular elastance, as indicated by the fact that LV pressure is decreasing despite an increase in LV volume.

To allow meaningful comparisons from patient to patient despite the wide variations in ventricular volume and wall thickness, it appeared useful to analyze this phase starting at an identical level of wall stress rather than starting at an identical level of pressure or wall strain. Indeed, computations of strain require exact knowledge of the ventricular dimension at zero wall stress, a datum unavailable in patients. The selected procedure ensured that a common level of residual systolic wall tension was present in all patients studied; nevertheless, despite large changes in ventricular size, this common level generally occurred at comparable ventricular pressure in normal subjects and in those with valve disease. This finding suggests that in many patients the increased wall thickness largely compensated for the deleterious effects of cardiac dilatation. Empirically, we found that a value around 40 kdyne/cm^2 (range 30 to 50) was appropriate because it was present in all patients during this phase. Starting from the pressure and volume data producing a stress of about 40 kdyne/cm^2, the incremental LV elastance was then computed using a standard increase in volume (20 ml/m^2).

Incremental elastance was preferred to the absolute value of elastance (pressure/volume [P/V]) or to the first derivative of elastance (d[P/V]/dt) (Fig. 1) because the values of incremental elastance ($\Delta P/\Delta V$) are not influenced by absolute ventricular volume. In contrast, both elastance and its first derivative greatly depend on the ventricular geometry at which they are determined and are abnormal in all patients with an enlarged heart, regardless of myocardial function. Because this index was new, we decided to determine whether it was sensitive enough to show the abnormalities in ventricular relaxation often present in patients with coronary heart disease.[12,15,16,19–21] Table II indicates that both indexes were abnormal in this group. Furthermore, the patients with coronary heart disease and abnormal incremental elastance also had an abnormal time constant of isovolumic pressure decrease[16,19] and an abnormal first-third filling fraction.[20]

Several problems arise when computing (as in the present study) the incremental elastance directly from the raw angiographic data without any interpolation between frames. This method does not always provide a frame with the starting stress required. Consequently, some variations in starting stress and volume increments (Table II) were unavoidable, and this certainly contributed to some extent to the variations in the calculated elastance as well as in the calculated changes in velocity of lengthening. The use of a filtering process allowing interpolations between frames certainly could improve the precision of the computed indexes. Finally, because a 20 ml/m^2 volume increment was arbitrary, the values of incremental elastance derived from a 10 ml/m^2 volume change were also studied. Similar conclusions could be drawn from this index. In addition, it even appeared more sensitive: The average incremental elastance with use of a ΔV = 10 ml/m^2 was −1.96 mm Hg/ml per m^2 in normal subjects and −0.79 in patients with valve disease ($p < 0.01$). The changes in wall stress (−25 versus −12 kdyne/cm^2; $p < 0.01$) and in velocity of lengthening (+1.94 versus +0.26 circ/s; $p < 0.01$) during this period also differed between the 2 groups. However, the value of this other index could not be obtained in more than 30% of the patients because the changes in ventricular volume between angiographic frames exceeded 10 ml/m^2 during this period of decreasing elastance. Accordingly, a volume increment of at least 20 ml/m^2 was preferred, but the use of angiographic techniques with a higher frequency response should probably provide a better estimation of the ventricular elastance.

Significance of the changes in incremental elastance and velocity of lengthening during the early diastolic filling phase: Among the different factors determining the diastolic properties of the left ventricle,[24,36] 4 should be considered in interpreting our observations: the passive elasticity,[36] the active relaxation process,[8,13,17,18,23,24] the viscous properties,[34,35,37,38] and finally, the restoring forces[39] that represent the elastic recoil of the myocardium. In our study the influence of the passive elastic properties is probably negligable, as indicated by the fact that both LV pressure and wall stress were decreasing during the increase in ventricular volume.

In contrast, the relaxation process is likely to play a major role during this diastolic phase, and several arguments favor the hypothesis that the changes in both indexes observed in the present study indeed reflect an impaired ventricular relaxation. However, it is well known that relaxation is a load-dependent phenomenon,[6,7,10,11] and we observed some correlations between an increased afterload and the values of incremental elastance. A slower relaxation caused by a greater afterload of the myocardium might therefore partly explain the variations in incremental elastance observed between normal subjects and patients with valve disease (Fig. 4). However, changes in inotropic state also greatly modify myocardial relaxation,[2,6–8,11,19] a decrease in inotropic state being generally attended by a slower relaxation. Patients with valve disease and a normal index of myocardial contractility generally had a normal incremental elastance, whereas those with a depressed index of contractility had impaired indexes (Fig. 5). It is therefore logical to propose that the changes in incremental elastance and in velocity of lengthening evidenced in this study were mainly caused by impaired LV relaxation. Furthermore, a reasonable hypothesis to explain this impaired relaxation is a depressed myocardial contractility in these patients.

However, factors other than the active relaxation process, such as the viscous properties or the restoring forces, might also explain these changes in ventricular elastance. The filling rates were higher in patients with valve disease than in normal subjects during this phase

(average values 412 versus 214 ml/s per m^2; $p < 0.01$), and these high filling rates certainly increased the viscous resistance in this setting. In addition, the viscous properties of the myocardium are known to increase with length in isolated muscle and in animals,[35,37] a finding that was recently confirmed in man.[38] Because the end-systolic volume is much greater in patients with valve disease (Table I), their early diastolic filling starts at a greater muscle length, and consequently the viscous effect is expected to be greater in such patients. Similarly, the elastic recoil of the myocardium is also expected to be reduced when the end-systolic volume is augmented, and this factor might also play a role in the observed changes. Finally, the possibility that the viscous properties of the hypertrophied myocardium could be abnormal should also be considered.

In summary, our data indicate that an impairment of LV elastance during early diastole generally is associated with changes in ventricular afterload and inotropic state. A large number of patients with apparently normal ventricular function still have normal incremental elastance, which can explain the overlap of incremental elastance among groups. Further studies are needed to clarify the respective roles of the active relaxation process, of the viscous properties, and of the restoring forces in determining these diastolic abnormalities.

Clinical implications: Effects of nifedipine: Our data indicate that at least 50% of the patients studied (Fig. 3) have impaired ventricular elastance during early diastole. The clinical implications of these observations are twofold. First, previous studies have suggested that similar abnormalities in early diastolic filling contributed to the patients' functional symptoms[14,17,18,22] and that interventions such as the administration of a calcium antagonist might improve these abnormalities and the patients' functional status.[17,18,22] In this perspective, our data indicate that the sublingual administration of nifedipine significantly enhanced the early diastolic properties (Fig. 1, Table III) together with the ejection fraction and the mean velocity of fiber shortening. Our findings also suggest that these beneficial effects might be related to a decreased afterload (−20 mm Hg in LV systolic pressure [$p < 0.01$] and −17% in peak wall stress [$p < 0.05$]) rather than to an increase in inotropic state. The index of inotropic state in our study was slightly depressed after administration of nifedipine. Accordingly, therapeutic interventions with afterload-reducing agents might deserve further investigations in patients with valvular regurgitation. These effects of nifedipine also support the hypothesis that incremental elastance mainly reflects ventricular relaxation. It is unlikely that nifedipine could acutely modify myocardial stiffness or viscosity. However, a decrease in afterload was expected to improve incremental elastance by accelerating relaxation.

Second, other studies have suggested that abnormalities of diastolic properties might be useful in detecting irreversible myocardial damage.[40] Therefore, it might be worthwhile to investigate postoperatively this diastolic phase in all patients with previously impaired ventricular elastance, After valve replacement, such an assessment could be easily performed noninvasively.[19,20–22]

In conclusion, our data indicate that a standardized index of LV elastance, computed during early diastolic filling, is abnormal in at least 50% of patients with valvular regurgitation. This approach is also able to detect abnormalities in diastolic filling in patients with heart disease. This index might therefore be useful in understanding the changes in myocardial function after valve surgery.

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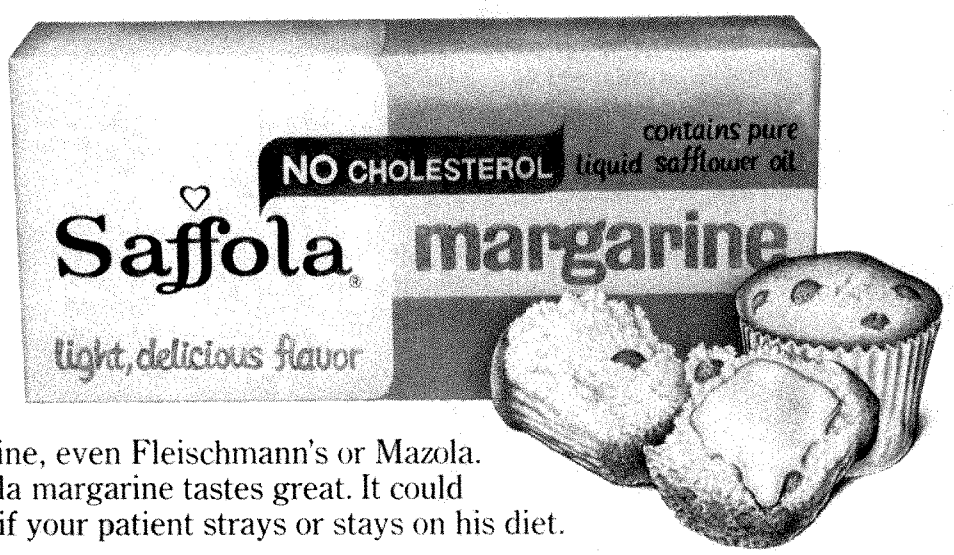

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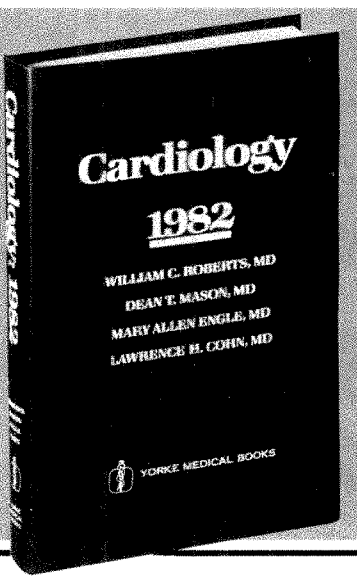

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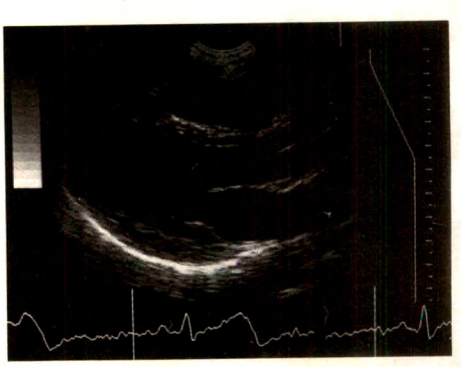

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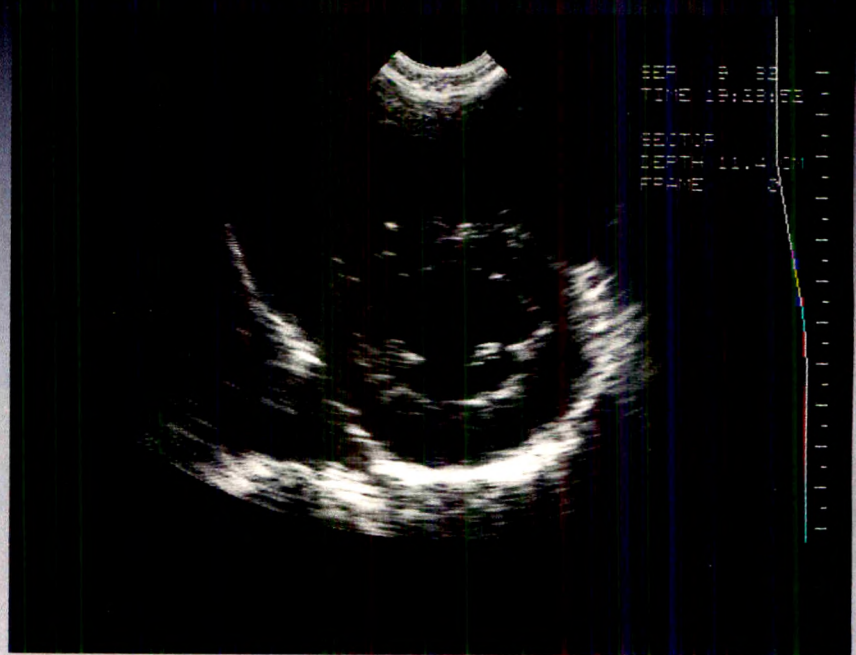

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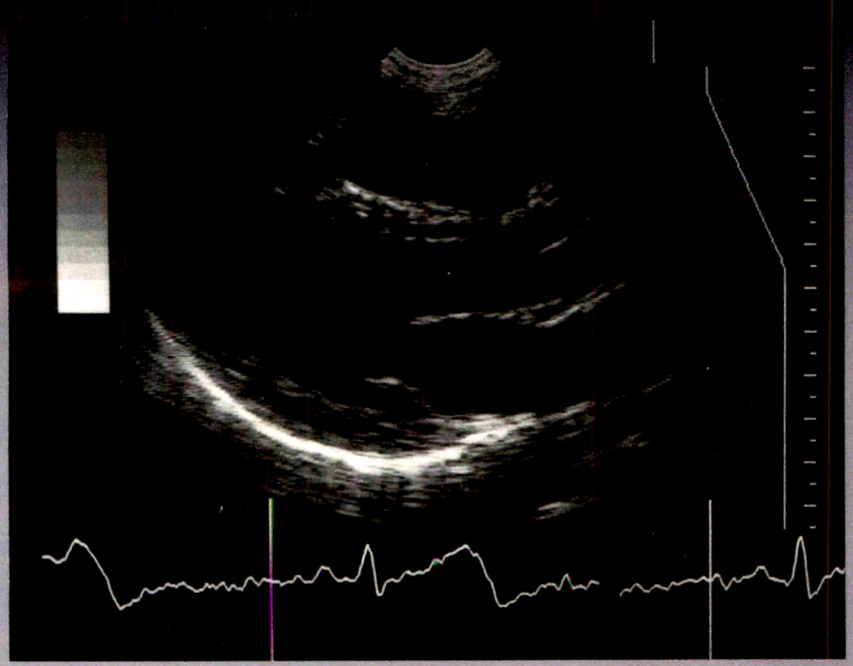

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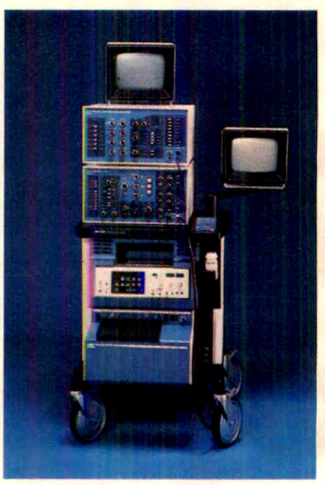

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Detection of Mild Aortic Regurgitation by Range-Gated Pulsed Doppler Echocardiography

RICARDO J. ESPER, MD

In order to assess the sensitivity and specificity of the range-gated pulsed Doppler echocardiogram for the detection of aortic regurgitation, a study with use of this technique was carried out in 46 patients. They were classified into 3 groups: *Group I* was composed of 19 patients with a variety of heart diseases but with a competent aortic valve. Cardiac catheterization revealed no aortic regurgitation in any of the 19 patients, and the Doppler echocardiogram detected no turbulent diastolic flow in the left ventricular outflow tract. *Group II* was composed of 17 patients who clinically and by auscultation had aortic regurgitation, which was confirmed by cardiac catheterization in 6. In all 17 patients the Doppler echocardiogram detected several grades of turbulent diastolic flow compatible with aortic regurgitation in the left ventricular outflow tract. *Group III* was composed of 10 patients with aortic regurgitation but without the expected clinical or auscultatory evidence. The echocardiogram detected mitral valve flutter in only 1 patient. Cardiac catheterization revealed aortic regurgitation graded 1/4 and 2/4 in 9 patients, and the patient who did not undergo catheterization had a murmur of aortic insufficiency 6 months later. In all 10 patients the Doppler echocardiogram detected a regurgitating turbulent flow compatible with aortic regurgitation in the left ventricular outflow tract.

It is concluded that the Doppler echocardiogram was more useful than auscultation and echocardiography for the detection of mild aortic regurgitation. In this study the range-gated pulsed Doppler echocardiogram proved 100% sensitive and specific. However, it will be necessary to study larger groups in order to assess its utility in more complicated conditions (obesity, emphysema, and heart failure) and the differential diagnosis with other diastolic murmurs.

Aortic valve insufficiency produces a variety of characteristic signs that are well known, but the most reliable sign is auscultation of an early diastolic murmur in the left parasternal area. However, on some occasions the characteristic murmur and peripheral signs are absent.[1-3] In these cases echocardiography may prove useful when it reveals diastolic flutter of the anterior leaflet of the mitral valve or of the left side of the interventricular septum,[4,5] but these findings are not consistent and aortography is required to make the diagnosis.[6] Under these circumstances, range-gated pulsed Doppler recording combined with either M-mode or 2-dimensional echocardiography may demonstrate the existence of pathologic diastolic turbulent flow in the left ventricular outflow tract below the aortic valve level, which can spread to the apex in cases of increased severity.[7]

The aim of the present study was to assess the sensitivity and specificity of the range-gated pulsed Doppler echocardiogram in the detection of pathologic diastolic subaortic turbulent flow in a group of patients with aortic insufficiency without an audible diastolic murmur. The findings were compared with findings in another group of patients with aortic insufficiency with a characteristic diastolic murmur. A third patient group without aortic insufficiency served as the control group.

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Methods

Study Patients

Forty-six patients classified into 3 groups were included in the study (Table I).

Group I: Competent aortic valve: The control group was composed of 19 patients, both male and female, affected by diverse forms of cardiopathy. None had clinical, auscultatory,

TABLE I Characteristics of the Patients Studied

Case	Diagnosis	Age (yr) & Sex	Aortic Valve Regurgitation: Ao Diast Murmur	Echo M Flutter	Graded Angio	Doppler Tur Flow	Clinical Severity
			Patients Without Aortic Regurgitation				
1	CHD	49M	No	No	No	No	. . .
2	CHD	52M	No	No	No	No	. . .
3	CHD	47M	No	No	No	No	. . .
4	CHD	53M	No	No	No	No	. . .
5	CHD	55M	No	No	No	No	. . .
6	CHD	46M	No	No	No	No	. . .
7	CHD	41M	No	No	No	No	. . .
8	M prolapse	42F	No	No	No	No	. . .
9	M prolapse	45F	No	No	No	No	. . .
10	IHSS	23F	No	No	No	No	. . .
11	IHSS	34M	No	No	No	No	. . .
12	Rheumatic MS	27F	No	No	No	No	. . .
13	Rheumatic MS	42F	No	No	No	No	. . .
14	Rheumatic MR	29F	No	No	No	No	. . .
15	Ao stenosis	52M	No	No	No	No	. . .
16	Ao stenosis	59F	No	No	No	No	. . .
17	Ao prosthesis	24M	No	No	No	No	. . .
18	Ao prosthesis	42M	No	No	No	No	. . .
19	Ao prosthesis	58F	No	No	No	No	. . .
			Patients With Aortic Regurgitation and With Aortic Diastolic Murmur				
20	Rheumatic MS	36M	Yes	Yes	3/4	Yes	Severe
21	Rheumatic MS	38F	Yes	Yes	. . .	Yes	Moderate
22	Rheumatic MS	41M	Yes	Yes	. . .	Yes	Moderate
23	Rheumatic MS	37M	Yes	No	. . .	Yes	Moderate
24	Rheumatic MS	19F	Yes	No	. . .	Yes	Moderate
25	Endocarditis	46M	Yes	Yes	3/4	Yes	Severe
26	Endocarditis	42M	Yes	Yes	. . .	Yes	Mild
27	Bicuspid Ao	17M	Yes	Yes	3/4	Yes	Severe
28	Bicuspid Ao	36M	Yes	No	. . .	Yes	Mild
29	Marfan syndrome	42M	Yes	Yes	. . .	Yes	Moderate
30	Ao prosthesis	28M	Yes	No	2/4	Yes	Mild
31	Ao prosthesis	32M	Yes	Yes	2/4	Yes	Moderate
32	Ao prosthesis	44F	Yes	No	. . .	Yes	Mild
33	Undetermined	43M	Yes	Yes	. . .	Yes	Moderate
34	Undetermined	21F	Yes	No	. . .	Yes	Mild
35	Undetermined	26M	Yes	Yes	3/4	Yes	Severe
36	Undetermined	56F	Yes	No	. . .	Yes	Mild
			Patients With Aortic Regurgitation and Without Aortic Diastolic Murmur				
37	Rheumatic MS	38F	No	No	1/4	Yes	Nondiagnosed
38	Rheumatic MS	42F	No	No	1/4	Yes	Nondiagnosed
39	Rheumatic MS	46F	No	No	1/4	Yes	Nondiagnosed
40	Rheumatic MS	23F	No	No	2/4	Yes	Nondiagnosed
41	Calcified Ao S	53M	No	No	1/4	Yes	Nondiagnosed
42	Calcified Ao S	40F	No	No	1/4	Yes	Nondiagnosed
43	Bicuspid Ao	39M	No	Yes	1/4	Yes	Mild
44	Ao prosthesis	29M	No	No	1/4	Yes	Nondiagnosed
45	Ao prosthesis	42F	No	No	1/4	Yes	Nondiagnosed
46	Ao prosthesis	52M	No	No	. . .	Yes	Nondiagnosed

Angio = angiography; Ao = aortic valve; CHD = coronary heart disease; Diast = diastole; IHSS = idiopathic hypertrophic subaortic stenosis; M = mitral valve; R = regurgitation; S = stenosis; Tur flow = turbulent aortic regurgitant flow.

echocardiographic, or hemodynamic evidence of aortic valve regurgitation. Three of the patients had a prosthetic aortic valve; 2 were of the porcine type[8] (Cases 18 and 19) and 1 was of the dura mater type[9] (Case 17). In the 2 patients with aortic stenosis the cause was undetermined; the aortic valve gradient was 65 and 80 mm Hg, respectively. No patient had heart failure.

Group II: Aortic regurgitation with characteristic physical findings: This group was composed of 17 patients, both male and female, with chronic aortic insufficiency either isolated or in association with other abnormalities. They were classified clinically as mild, moderate, and severe, according to New York Heart Association functional criteria.[10] All had a regurgitant diastolic murmur characteristic of aortic insufficiency with amplitudes varying between grades 2/6 and 5/6.[11] Six of the 17 patients underwent cardiac catheterization which revealed aortic regurgitation graded 2/4 and 3/4, respectively.[12]

Three of the patients (Cases 20, 21, and 24) had associated mitral stenosis. Three other patients had a prosthetic valve of the biologic type in the aortic position; 2 of them were made of dura mater, and had been placed 4 and 5 years earlier (cases 30 and 31), and the third, a porcine valve, had been placed 8 months earlier.

Group III: Aortic regurgitation without detectable physical signs: This group was composed of 10 patients examined by at least 2 experienced cardiologists, but without any clinical signs suggesting aortic insufficiency. None had

a diastolic murmur of aortic regurgitation, in the supine or standing position, during deep expiration or during hand-grip test. Nine underwent cardiac catheterization, which revealed grade 1/4 regurgitation, except for 1 patient (Case 40) with grade 2/4 reflux. The 10th patient (Case 46) who did not undergo catheterization was later found to have a murmur of aortic insufficiency 6 months after this study was done.

Doppler Echocardiography

A range-gated pulsed Doppler examination was carried out in these 46 patients by the same physician using a commercially available instrument (Mark V, Advanced Technology Laboratories, Seattle, Washington) which makes it possible to obtain a Doppler recording along the same ultrasonic beam as the echocardiogram and from a teardrop-shaped region, called the sample volume. This point is positioned in the affected area by means of 2-dimensional echocardiographic imaging. The Doppler flow signal can be obtained in 2 ways: (1) through an auditory signal that makes it possible to differentiate between the soft sound of the laminar flow and the harsh sound of the pathologic turbulent flow, and (2) through a graphic recording that shows both the M-mode echocardiogram on which is superimposed a depth line indicating the location of the sample volume and the spectral time-interval histogram, where the different frequencies of the reflected ultrasonic beam are diagrammed like dots in a system of coordinates with respect to time. Laminar flows produce a dot pattern that inscribes a smooth curve, whereas turbulent flows generate a dispersed dot pattern, similar to the recording of murmurs in a phonocardiogram.[13,14] As in all recordings, the amplitude of the signals varies according to the selection of the Doppler instrument's threshold and gain controls. Thus both the experience of the operator and the standard values established by the laboratory are important. The lowest effective threshold was used together with a gain setting that would exclude excessive electronic noise.[15,16] Care was taken to limit the amplitude of the Doppler signal (lower tracing in all the figures) to show peaks and not plateaus; for this reason the controls were continuously adjusted for each patient to produce consistent results.[17–19] Flow was considered turbulent when the features of the auscultatory signals were characteristic, and if at the same time the dotted pattern of the time-interval histogram was over 1 cm wide.

Technique: The Doppler echocardiographic examination was of acceptable technical quality in all patients and was carried out no more than 2 weeks before catheterization. The patient's position varied from supine to semidecubitus or left lateral decubitus. First a 2-dimensional echocardiogram was performed scanning the long axis in the parasternal area with conventional techniques already reported.[20,21] Then a complete scan of the left ventricle by the M-mode method was obtained, and finally the Doppler flow signals were studied in the left ventricular inflow and outflow tracts as well as the aortic root. Special care was taken in studying the outflow tract of the left ventricle below the aortic valve, where a smooth systolic flow with features similar to those of the aortic root is usually obtained. In cases of aortic stenosis the systolic flow is turbulent, whereas in aortic insufficiency a harsh, turbulent, regurgitating diastolic flow can be appreciated from the audio signal and recorded graphically.[7] Special care was taken to avoid sampling near the aortic and mitral valves so as to avoid the clicks that are characteristic of the movement of these valves.[13,14] Mitral stenosis produces a turbulent diastolic flow in the left ventricular inflow tract which—when it is very intense—may be detected in the outflow tract and mistaken for aortic regurgitation. In these cases, special care was taken to place the sample volume and to assess the timing and auditory characteristics of the Doppler signal. In aortic regurgitation the signal appears earlier and decreases during diastole, whereas in mitral stenosis the auditory signals usually appear later and are sustained during the entire diastole. Since from the parasternal area the sample volume may be laid perpendicularly to the blood flow velocity and therefore no Doppler signal may be recorded, we proceeded to scan the left ventricular outflow tract and aortic root from the suprasternal area in all cases.

Cardiac catheterization: Catheterization was performed according to conventional methods and angiography was performed injecting contrast material into the aortic root. Special care was taken in the positioning of the catheter as well as in the pressure of the injection of contrast medium to avoid false aortic regurgitation produced by technical shortcomings. The severity of regurgitation was graded 0 to 4.[12]

Results

The patients in group I by definition lacked any clinical, auscultatory, or echocardiographic evidence of aortic regurgitation. Cardiac catheterization revealed no valve reflux (Table I).

In group II all the patients had a regurgitant diastolic murmur characteristic of aortic insufficiency. They were classified as mild, moderate, and severe according to the clinical, radiologic, and electrocardiographic findings. Cardiac catheterization confirmed aortic insufficiency in 6 patients, and the diagnosis was amply supported in other patients by noninvasive methods (Table I).

Group III was composed of patients with no clinical or auscultatory signs suggesting aortic regurgitation, except for 1 patient whose echocardiogram revealed the existence of mitral valve flutter. In 3 patients (Cases 37, 38, and 41) the diagnosis was made first by cardiac catheterization and after further reassessment the Doppler echographic examination revealed pathologic turbulent flow, characteristic of aortic regurgitation, in the left ventricular outflow tract. In the remaining 7 patients (Cases 39, 40, and 42 to 46) the diagnosis was obtained by Doppler echographic examination and was later confirmed by cardiac catheterization in 6.

Echocardiography—mitral valve flutter: In group I there was no evidence of mitral valve flutter. In group II 10 patients or 58.8% of the 17 patients exhibited mitral valve flutter. In group III only 1 patient (Case 43) demonstrated mitral valve flutter; this led to the presumption of aortic regurgitation, which was described as mild, and angiography detected a reflux graded 1/4.

Catheterization data: In group I no aortic reflux was noted in any of the 19 patients, which confirmed the clinical presumption. In group II only 6 patients had angiographic studies that revealed aortic regurgitation with severity graded 2/4 and 3/4. The other patients did not have hemodynamic studies because noninvasive diagnostic evidence was considered adequate, or valve insufficiency was too mild to warrant invasive studies. In the third group 9 patients underwent angiography revealing aortic regurgitation graded 1/4, except for 1 patient (Case 40) graded 2/4.

Doppler examination: In group I the Doppler examination revealed no pathologic turbulent diastolic flow in the left ventricular outflow tract either on

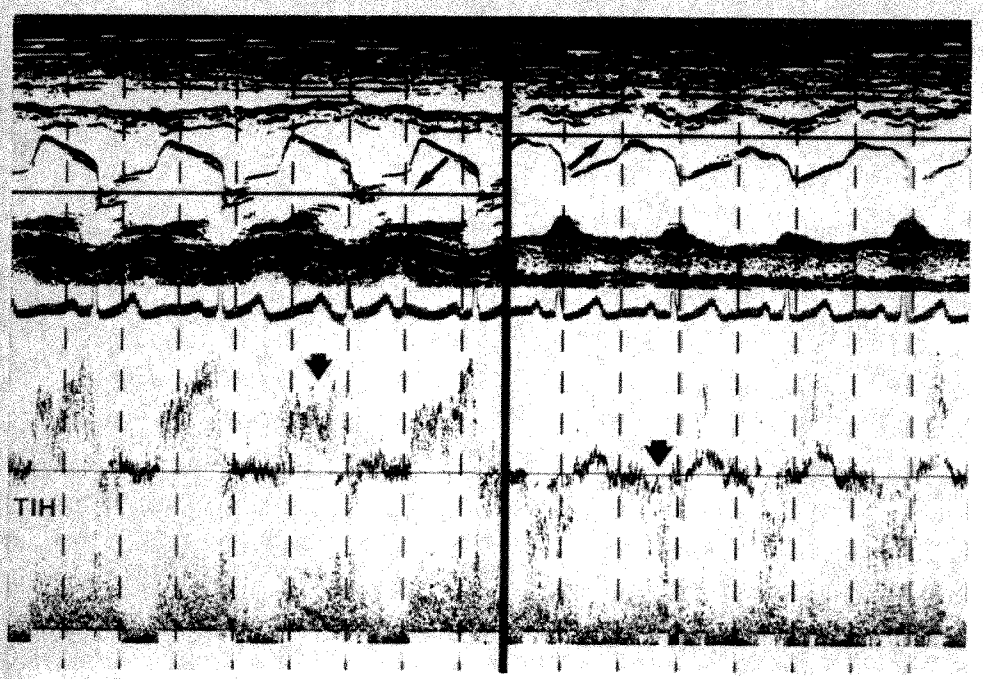

FIGURE 1. Patient 37 with rheumatic mitral stenosis and aortic insufficiency. **Left,** the sample volume (**thin arrow**) is placed in the left ventricular inflow tract, in front of the mitral valve, and the time interval histogram (TIH) shows turbulent flow of mitral stenosis (**thick arrow**). **Right,** the sample volume is placed in the left ventricular outflow tract (**thin arrow**) and a turbulent flow of aortic regurgitation is shown (**thick arrow**) in the time interval histogram.

scanning the parasternal area or from the suprasternal area. The 2 patients with aortic stenosis (Cases 15 and 16) and the 2 patients with idiopathic hypertrophic subaortic stenosis (Cases 10 and 11) exhibited turbulent systolic flow in the aortic root and in the left ventricular outflow tract. One of the patients with mitral valve prolapse (Case 8) and another with rheumatic mitral insufficiency (Case 14) exhibited turbulent harsh systolic flow in the left atrium near the mitral valve, and the 2 patients with mitral stenosis (Cases 12 and 13) had pathologic diastolic turbulent flow in the left ventricular inflow tract that did not spread into the outflow tract. The patients with biologic aortic prosthetic valves (Cases 17 to 19) had a mild turbulent flow in the aortic root, but it was not severe enough to be considered pathologic. The 7 patients with coronary heart disease (Cases 1 to 7) did not display pathologic turbulence.

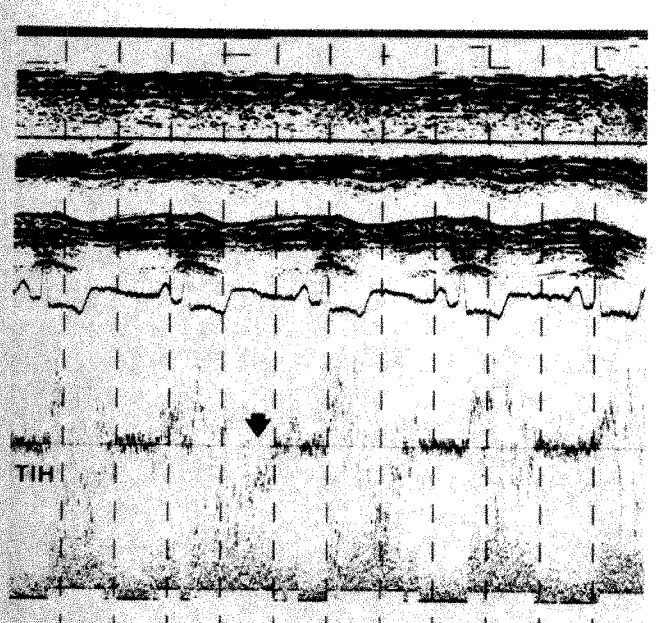

FIGURE 2. Patient 41 with calcified aortic stenosis. The sample volume (**thin arrow**) is placed in the aortic root above the aortic valve from suprasternal view. The time interval histogram (TIH) shows turbulent systolic flow of aortic stenosis and diastolic regurgitant flow of aortic insufficiency (**thick arrow**).

In group II all patients had diastolic turbulence in the left ventricular outflow (100%) detected from both the parasternal and suprasternal areas. In some of them the flow extended to the apex. The patients with mitral stenosis also had turbulent flow in the left ventricular inflow tract, distinct in timing and characteristics from that of aortic regurgitation. The 2 patients with an aortic congenital bicuspid valve (Cases 27 and 28) and those with an aortic prosthetic valve (Cases 30 to 32) revealed systolic turbulence that was too low in amplitude to be regarded pathologic.

In group III all patients showed a mild diastolic turbulence in the left ventricular outflow tract detected from both the parasternal and suprasternal areas. The 4 patients with added mitral stenosis (Cases 37 to 40) also had diastolic turbulence in the left ventricular inflow tract, distinct from that produced by aortic reflux (Fig. 1). The 2 patients with calcific aortic stenosis had clear pathologic systolic turbulent flow, but neither the patient with congenital aortic bicuspid valve (Case 43) nor the ones with aortic prosthetic valve revealed pathologic systolic flow patterns (Fig. 2).

Discussion

In aortic valve insufficiency, the regurgitant blood flow generates turbulence which produces the diastolic murmur that is the hallmark of this disease. However,

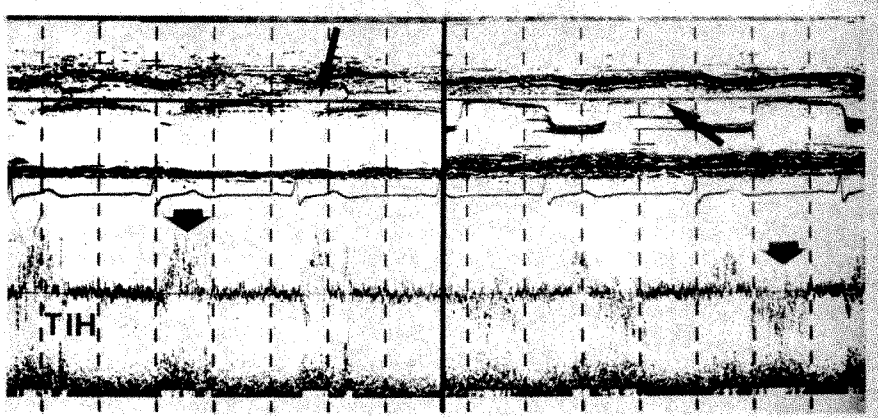

FIGURE 3. Patient 39 with rheumatic mitral and aortic valvulopathy. **Left,** the sample volume is placed in the aortic root, through the aortic valve (**thin arrow**), showing systolic aortic turbulent flow (**thick arrow**) in the time interval histogram (TIH). **Right,** the sample volume is in the left ventricular outflow tract (**thin arrow**), showing a turbulent diastolic flow of aortic regurgitation (**thick arrow**) in the time interval histogram.

in mild regurgitation the murmur may not be heard, especially in patients who are obese or have pulmonary emphysema.[1,3] The murmur may also diminish in cases of left ventricular failure when the reduction in left ventricular compliance and the increase in left ventricular end-diastolic pressure reduce the regurgitation. In cases of mitral stenosis or severe aortic stenosis the clinical and auscultatory signs of aortic insufficiency may be concealed or altered so as to become inapparent.[1–3] Thus, mild aortic insufficiency with atypical clinical manifestations and no audible murmur may go unnoticed or turn up as a chance finding in cardiac catheterization.[6]

The range-gated pulsed Doppler echocardiogram allows detection of turbulence of the bloodstream in the left ventricular outflow tract produced by regurgitation.[7] Turbulence, in turn, is thought to be the cause of the murmurs. The limitations that may prevent our obtaining a technically useful echocardiogram are also operative for the Doppler examination. In the present study only those patients who had a satisfactory Doppler echocardiogram were included. However, no patient was extremely obese and none had pulmonary emphysema, which might have suppressed the auscultatory phenomena.

Diagnostic role of Doppler echocardiogram in the absence of a diastolic murmur: It might be assumed that the aortic insufficiency in the patients in group III was very mild and therefore no murmur could be heard. However, 1 patient (Case 40) exhibited angiographic aortic regurgitation graded 2/4, and another (case 43) had mitral valve flutter in the echocardiogram. In contrast, 5 patients in group II (Cases 26, 28, 30, 32, and 34) had aortic insufficiency that might be described clinically as mild (that is, without electrocardiographic or radiologic abnormalities and with a diastolic murmur of aortic insufficiency as the only finding). Only 1 of these patients (Case 26) had mitral valve flutter in the echocardiogram (20% of the mild cases). This finding leads to the assumption that in patients in group III, the sound energy produced by the turbulence of the regurgitating jet was not intense enough to produce an audible murmur. Furthermore, all the patients in group III were examined by at least 2 experienced cardiologists, and the additional examinations were carried out retrospectively to make certain that minimal signs had not been overlooked. Reinforcement of the suspected murmur signs was produced by altering the patient's position and respiration and by hand-grip exercise. Although phonocardiographic records were obtained, these were not mentioned because it is well known that in the specific case of aortic insufficiency, murmurs are not always recorded because of their high pitch and low intensity, the human ear being more sensitive.

In the patients in our study, the various cardiac abnormalities other than aortic regurgitation that were encountered such as mitral stenosis, mitral insufficiency, aortic stenosis, mitral valve prolapse and idiopathic hypertrophic subaortic stenosis yielded Doppler records, all of which were characteristic and consistent with the clinical diagnoses and cardiac catheterization findings. This observation led to the assumption that the technique that was used was satisfactory in these assorted groups of patients for the correct diagnosis of their complaints (Fig. 3).

Assessing the severity of aortic regurgitation: Other investigators have been able to assess the direction of the jet and the severity of regurgitation in patients with mitral insufficiency by scanning the left atrium with the sample volume of the range-gated pulsed Doppler recording.[22,23] In aortic insufficiency it is possible to have an idea of the severity by detecting the dispersion or distribution of the turbulent regurgitating flow. In mild cases it confines itself to the left ventricular outflow tract, in moderate cases it invades the inflow tract, and in severe cases it can reach the apex.[24] But this exploration encounters certain restrictions and demands that no other valve disease exist (as in the case of mitral stenosis in which the jets overlap) and that the left ventricle be dilated in such a way as to prevent the anterior leaflet of the mitral valve from contacting the interventricular septum and hindering the scanning of the sample volume. The possible impact of these factors could not be studied in the present investigation. However, in all patients in group III the turbulence was confined to the left ventricular outflow tract, suggesting that regurgitation was mild in all.

Associated abnormalities: Probably some associated pathologic conditions favor the detection of diastolic turbulent flows resulting from aortic regurgita-

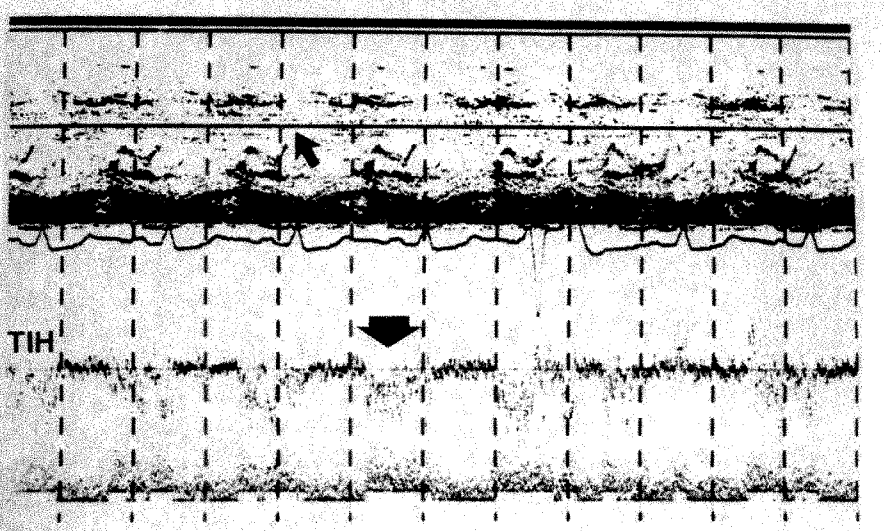

FIGURE 4. Patient 46 with a biologic aortic prosthesis, who had an audible murmur of aortic regurgitation after 6 months. The sample volume (**thin arrow**) is placed in the left ventricular outflow tract, and the time interval histogram (TIH) shows a turbulent flow of aortic regurgitation (**thick arrow**).

tion, whereas other conditions have a detrimental effect. In the present study, however, patients in groups I and II had associated valve conditions similar to those of group III, such as mitral stenosis, mitral insufficiency, aortic stenosis, congenital bicuspid aortic valve, and biologic prostheses of dura mater and porcine valve. It is widely assumed that mitral stenosis hinders the recording of aortic insufficiency by range-gated pulsed Doppler examination. However, in these patients it was possible to discern both flows (Fig. 1).

Doppler recording versus auscultation: One patient in group III (Case 46) had a characteristic diastolic murmur of aortic regurgitation that was heard in a routine check-up 6 months after the first Doppler echographic examination. Results suggested that damage to the prosthetic valve was progressive, thus generating an increase in the sound energy so as to make the murmur audible (Fig. 4). In the same way, a mild but distinct murmur of aortic insufficiency was heard in another patient (Case 39) with mitral stenosis 8 months after operation.

The patients in group II who were diagnosed as having aortic insufficiency without confirmation by cardiac catheterization require a word of explanation. Auscultation demonstrated the typical murmur. The physicians in charge rejected the option of catheterization because the leak was considered mild. Isolated pulmonary valve regurgitation, a rare cause of a similar murmur, was considered highly unlikely. It may be concluded that both the Doppler recording and auscultation detect the same phenomenon; however, the Doppler recording proved more sensitive in detecting turbulence in the left ventricular outflow tract.

In the present study the 19 patients in group I, clinically and angiographically proved without aortic insufficiency, had no turbulence in the left ventricular outflow tract according to the Doppler recording, whereas all 17 patients in group II with aortic insufficiency had reflux. In group III all patients had mild aortic insufficiency (grade 1/4) except for 1 with moderate insufficiency (grade 2/4), but none had an audible diastolic murmur of regurgitation. The Doppler recording, however, proved useful in detecting the diastolic turbulent flows in all patients.

Clinical implications: Our findings give the range-gated pulsed Doppler echocardiogram a 100% sensitivity and specificity capacity for the detection of aortic insufficiency. However, it would be presumptive to claim that the method is 100% sensitive and specific in all instances without further evidence. In this study the 49 patients were selected because a technically adequate Doppler echocardiogram could be obtained. Patients were neither obese nor emphysematous, and those with heart failure were excluded.

It will be necessary to carry out studies with larger groups to ascertain the ultimate sensitivity and specificity of the method, but in our hands the range-gated pulsed Doppler echocardiogram proved far more sensitive than auscultation and echocardiography for the detection of mild aortic valve regurgitation. The detection of paravalve regurgitation and the utility of the method for differential diagnosis from other diastolic murmurs with similar features still remain to be assessed.

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Large V Waves in the Pulmonary Wedge Pressure Tracing In the Absence of Mitral Regurgitation

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The accurate diagnosis of mitral regurgitation has important therapeutic implications. We have observed that large V waves in the pulmonary wedge pressure (PW) may be misleading in the diagnosis of mitral regurgitation. Of 237 consecutive patients with high quality hemodynamic, angiographic, and echocardiographic data, 27 had large V waves (peak V 10 mm Hg greater than pulmonary wedge mean pressure). Ventriculograms were analyzed in blind fashion by 3 expert angiographers for any angiographic evidence of mitral regurgitation; 17 patients had mitral regurgitation (group I), and 10 did not (group II). The control group (group III) of 22 patients had normal V waves and no mitral regurgitation. Twenty-two hemodynamic and echocardiographic variables were compared among groups. The only significant difference between groups I and II was in the slope of the ascent of the V wave (74.3 versus 141.9 mm/s, p = 0.021), also expressed as the mitral regurgitation index (6.01 versus 9.45, p = 0.005). A slope of 100 mm/s or slower had a sensitivity of 80% to confirm mitral regurgitation and a specificity of 70% to rule it out. The size of the V wave and the V/PW mean ratio were similar in groups I and II (38.5 ± 11 versus 37.5 ± 11 mm Hg, and 1.67 ± 0.3 versus 1.69 ± 0.4, respectively, p = NS) and were not helpful in predicting the presence or absence of mitral regurgitation. Among patients without mitral regurgitation (groups II and III), those with large V waves had a higher pulmonary wedge mean pressure (23.5 versus 15.6 mm Hg, p = 0.01), a higher A wave (25.3 versus 16.4 mm Hg, p = 0.032), a more elevated mitral regurgitation index (9.45 versus 3.99, p = 0.001), a larger left atrial size (24.5 versus 21.6 cc, p = 0.05), a greater V wave to pulmonary wedge mean pressure ratio (1.69 versus 1.10, p = 0.001), and a faster slope of ascent of the V wave (141.9 versus 53.05 mm/s, p = 0.005).

We conclude that large V waves in the pulmonary wedge pressure tracing can be seen in the absence of mitral regurgitation. The size of the V wave is related to factors that determine left atrial compliance. Caution is called for in the diagnosis of mitral regurgitation by pulmonary wedge pressure alone.

Hemodynamic monitoring is commonly used in the management of critically ill patients.[1,2] Information about the filling pressure of the left ventricle is obtained by evaluating the pulmonary wedge pressure or the pulmonary artery diastolic pressure.[3,4] Large V waves on this pulmonary wedge tracing are often interpreted as secondary to mitral regurgitation, and therapeutic decisions are based on this assumption.[5,6] We have observed a number of instances in which a large V wave recorded in the catheterization laboratory was not associated with angiographic or clinical mitral regurgitation.[7] The present study was designed to evaluate the prevalence of absent mitral regurgitation in patients with large V waves, and to gain some insight into the pathogenesis of a large V wave in the absence of mitral regurgitation.

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Methods

Study patients: All patients undergoing right and left heart catheterization with angiography in our laboratory between June 30, 1979 and December 31, 1980 were studied. There were 300 patients. Sixty-three were excluded for 1 or more of

the following reasons: (1) poor quality or absent pulmonary wedge tracing (damaged tracing, unclear calibration, etc.); (2) unavailable echocardiogram or tracings of suboptimal quality that did not allow precise measurements of the dimensions of the left atrium and left ventricle; or (3) absent or inadequate left ventriculogram for analysis of possible mitral regurgitation (premature ventricular beats, poor visualization of the area of the mitral valve and left atrium); and (4) presence of mitral regurgitation secondary to rupture of the mitral valve apparatus. Ruptured chordae or papillary muscle was diagnosed by clinical, hemodynamic, and angiographic variables, such as a murmur of mitral regurgitation that appeared suddenly, with typical echocardiographic findings, with a peaked, giant V wave and often with angiographic demonstration of a flail leaflet. Therefore, 237 patients remained in the study.

Patient groups: The study patients were divided into 2 groups according to the presence or absence of large V waves on the pulmonary wedge tracing. A large V wave defined by a peak pressure of 10 mm Hg or greater than the mean pulmonary wedge pressure was present in 27 patients. The groups were further divided according to the presence or absence of mitral regurgitation on the left ventriculogram: group I, large V wave with mitral regurgitation; group II, large V wave without mitral regurgitation. Of the remaining 210 patients, a random sample of 22 patients was used as the control: group III, normal V wave with no mitral regurgitation; and group IV, normal V wave with mitral regurgitation.

Measurements: Catheterization was performed in the postabsorptive state, under premedication with diazepam, 10 mg orally. Right heart catheterization was performed with a Swan-Ganz catheter, and pressures were recorded with an Electronics for Medicine DR 12 recorder at a paper speed of 50 and 100 mm/s. Fluid-filled lines and P23D Statham transducers were used. The mid-chest was used as a reference point for calibration of zero. Pulmonary wedge pressure was obtained by inflating the balloon of the Swan-Ganz catheter in the pulmonary artery and advancing it until wedge pressure was seen. If damped pressure was obtained, a new position was attempted and lines were carefully flushed. The A, V, and mean pulmonary wedge pressures were measured in millimeters of mercury. Cardiac output was determined by thermodilution with the Swan-Ganz catheter; a minimum of 3 measurements were averaged. Aortic and left ventricular pressures were also obtained with fluid-filled systems and P23D Statham transducers. Aortic and left ventricular systolic pressures were read as peak systolic pressures. Aortic diastolic pressure was measured at the lowest point in diastole. Left ventricular end-diastolic pressure was measured at the peak of the R wave on the electrocardiogram. The mitral regurgitation index was determined by the method of Libanoff and Rodbard[8]: mitral regurgitation index = (V wave ascent slope in mm Hg/0.02 second)/cardiac index (liters/min/m^2 body surface area). The slope of ascent of the V wave was calculated by dividing the height of the V wave in mm Hg by the time elapsed from the start to the peak of the V wave.

Cineventriculography: The procedure was performed in the 30° right anterior oblique and 60° left anterior oblique projections and filmed at 30 frames/s, using 40 ml of 76% Renografin® (meglumine diatrizoate). A steeper right anterior oblique projection was used when the spine overlapped the mitral valve in the 30° right anterior oblique view. The ventriculograms were reviewed independently by 3 expert angiographers, without knowledge of the clinical or hemodynamic data. Mitral regurgitation was defined as present when any amount of contrast agent was visualized in the left atrium during ventricular systole. Premature beats or postextrasystolic beats were not analyzed. Cases in which the quality of the ventriculogram was less than optimal or in which the area of the mitral valve and left atrium was not clearly visualized were excluded. The 3 observers agreed on the presence or absence of mitral regurgitation in all cases except 1; this case was eliminated from the study population. Ejection fraction was calculated using the formula: EF = (EDV − ESV) EDV, where ESV = end-systolic volume and EDV = end-diastolic volume; the area-length method[9] was used to calculate left ventricular volume.

Echocardiography: M-mode echocardiograms were obtained before catheterization in all patients, with an Irex Medical System at 50 mm/s paper speed. Left ventricular dimensions were measured according to the standard convention[10] which includes the endocardium in the measurement. Left ventricular diameter and thickness of the interventricular septum and left ventricular posterior wall were measured in diastole at the peak of the R wave on the electrocardiogram. Left ventricular wall stress was evaluated as peak systolic stress by the formula[11–13]: Peak stress = (SBP × LVID)/h × [1 + (h/LVID)], where SBP = systolic blood pressure, LVID = left ventricular internal dimension, and h = thickness of interventricular system plus posterior wall divided by 2. Left ventricular mass was calculated by the formula[14]: Left ventricular mass = 0.77×10^{-3} [(LVID + LVPW + IVS)^3 − LVID^3] + 2.4, where IVS = interventricular septal thickness and LVPW = left ventricular posterior wall thickness.

A ratio of left atrial dimension by echocardiography to mean pulmonary capillary wedge pressure was created to obtain an indirect index of the compliance of the left atrium. The ratio V wave/pulmonary wedge mean pressure was calculated to evaluate the relative size of the V wave.

Sensitivity was defined as the ability of a test to correctly identify mitral regurgitation. Sensitivity = true positive/(true positive + false negative). Specificity was defined as the ability of a test to correctly identify those without mitral regurgitation. Specificity = true negative/(true negative + false positive).

Statistical analysis: The data were stored and analyzed using SAS (Statistical Analysis System) on an IBM 370 computer at the City University of New York Computing Center. The group means were compared using analysis of variance and Duncan's multiple range test. Two-tailed *t* tests were also calculated between groups. When required, a 2-tailed *t* test for unequal variances was used. Observed probability levels less than 0.001 were reported as 0.001 in this study. Stepwise discriminant function analysis was used to determine what measurement or combination of measurements best discriminates between patients with a large V wave and mitral regurgitation and those with a large V wave without mitral regurgitation.

Results

Of the 27 patients with large V waves, 17 (63%) had mitral regurgitation on the left ventriculogram (group I) and 10 patients (37%) did not (group II). Of the 22 patients without a large V wave, none had mitral regurgitation (group III). There were no patients in group IV (normal V wave, mitral regurgitation present) as a result of the random distribution by chance.

Group II (large V wave, no mitral regurgitation) included 3 patients with mitral stenosis, 1 with aortic stenosis, 1 with aortic stenosis and mitral valve pros-

TABLE I Clinical, Hemodynamic, and Echocardiographic Characteristics in the 3 Groups*

	Group I	Group II	Group III
Patients (n)	17	10	22
Age (yr)	59.5 ± 12	56.2 ± 14	59.1 ± 10
Sex	10F, 7M	6F, 4M	7F, 15M
Atrial fibrillation	6/17	3/10	8/22
Aortic systolic pressure (mm Hg)	129.24 ± 25	143.90 ± 18	138.18 ± 31
Aortic diastolic pressure (mm Hg)	68.47 ± 15	69.0 ± 15	72.5 ± 11
LV systolic pressure (mm Hg)	143.12 ± 47	157.50 ± 38	157.82 ± 37
LVEDP (mm Hg)	19.88 ± 9	17.80 ± 7	17.82 ± 8.5
PW mean pressure (mm Hg)	23.53 ± 7	23.50 ± 8	15.64 ± 7
A wave (mm Hg)	25.30 ± 10	25.30 ± 8	16.40 ± 6.6
V wave (mm Hg)	38.53 ± 11	37.50 ± 11	16.91 ± 7.1
Cardiac index (liters/min/m^2)	2.47 ± 0.5	3.08 ± 1.1	2.64 ± 0.5
Ejection fraction (%)	58.71 ± 13	57.60 ± 21	58.32 ± 18
MRI	6.01 ± 2.3	9.45 ± 3.5	3.99 ± 1.4
V slope (mm/s)	74.3 ± 31.0	141.9 ± 75.5	53.05 ± 22.0
Left atrial dimension (mm)	26.1 ± 4.0	24.5 ± 4.0	21.6 ± 2.0
IVS (mm)	13.06 ± 3.8	12.40 ± 2.8	12.05 ± 2.2
LVPW (mm)	12.24 ± 3.0	12.10 ± 2.4	11.41 ± 1.6
LVID diastole (mm)	58.10 ± 12	56.20 ± 9	58.0 ± 0.7
LV mass (g)	351.19 ± 351	288.41 ± 123	261.10 ± 104.5
Peak stress	209.36 ± 64	231.94 ± 46	235.81 ± 50
LA size/PW mean (mm/mm Hg)	9.16 ± 2.7	9.73 ± 3.4	7.25 ± 3.3
V/PW mean ratio	1.67 ± 0.3	1.69 ± 0.4	1.10 ± 0.2

* Values are mean ± standard deviation. Group I = large V wave, mitral regurgitation; group II = large V wave, no mitral regurgitation; group III = normal V wave size, no mitral regurgitation.
EDP = end-diastolic pressure; IVS = interventricular septal thickness; LA = left atrium; LV = left ventricle; LVEDP = left ventricular end-diastolic pressure; LVID = left ventricular internal diameter; LVPW = left ventricular posterior wall thickness; MRI = mitral regurgitation index; PW = pulmonary wedge pressure; V = V wave.

thesis, 2 patients with aortic regurgitation, 2 with coronary artery disease, and 1 patient with patent ductus arteriosus.

Group III (normal V wave, no mitral regurgitation) included 4 patients with coronary artery disease, 7 with coronary artery disease and mild to moderate congestive heart failure, 1 with congestive cardiomyopathy, 1 with idiopathic hypertrophic cardiomyopathy, 4 with aortic stenosis, 3 with mitral stenosis, and 2 with aortic regurgitation.

Clinical hemodynamic, and echocardiographic data: Table I summarizes the clinical, hemodynamic, and echocardiographic data in group I (large V wave, mitral regurgitation), group II (large V wave, no mitral regurgitation), and group III (no large V wave, no mitral regurgitation). Table II shows the comparison of the 3 groups by Duncan's multiple range test. For each variable, the underlined groups have no statistically significant difference ($p < 0.05$).

Groups I and II, all with large V waves, were similar (without statistical significant difference) in the following variables (Table I): age, sex, incidence of atrial fibrillation, aortic systolic and diastolic pressures, left ventricular systolic and end-diastolic pressures, pulmonary wedge mean pressure, A and V wave height, cardiac index, ejection fraction, dimension of left atrium, left ventricular internal diameter, septal and posterior wall thickness by echocardiography, left ventricular mass, peak systolic stress, ratio of left atrial size to pulmonary wedge pressure, and the ratio V/pulmonary wedge mean pressure. The significantly different variables between groups I and II were the mitral regurgitation index (6.01 versus 9.45, $p = 0.005$) and the slope of ascent of the V wave (74.3 versus 141.9 mm/s, $p = 0.021$).

TABLE II Comparison Among the 3 Groups by Duncan's Multiple Range Test ($\alpha = 0.05$)

	Groups		
Age	I	II	III
Sex	I	II	III
Aortic systolic pressure (mm Hg)	I	II	III
Aortic diastolic pressure (mm Hg)	I	II	III
LV systolic pressure (mm Hg)	I	II	III
LVEDP (mm Hg)	I	II	III
PW mean pressure (mm Hg)	I	II	III
A wave (mm Hg)	I	II	III
V wave (mm Hg)	I	II	III
Cardiac index* (liters/min/m^2)	I	II	III
Ejection fraction (%)	I	II	III
MRI	I	II	III
V slope (mm/s)	I	II	III
Left atrial dimension (mm)	I	II	III
IVS (mm)	I	II	III
LVPW (mm)	I	II	III
LVID diastole (mm)	I	II	III
LV mass (g)	I	II	III
Peak stress	I	II	III
LA size/PW mean	I	II	III
V/PW mean ratio	I	II	III

* In addition, group I was different from group III ($p < 0.05$). Abbreviations as in Table I.

Slope of rise of V, mitral regurgitation index, and relative size of V wave (Fig. 1): To evaluate the best discriminatory value of a large V wave in proving or ruling out the presence of mitral regurgitation, we calculated the sensitivity and specificity of a continuous scale for (1) the slope of rise of the V wave, (2) the mitral regurgitation index, and (3) the relative size of the V wave (V wave/pulmonary wedge mean pressure ratio) (V/PW). Using the stepwise discriminant function procedure, the slope of ascent of the V wave was the measurement most useful in discriminating between

TABLE III Significant Correlations Between Size of the V Wave and Other Hemodynamic and Echocardiographic Variables

	Group I (n = 17)		Group II (n = 10)		Group III (n = 22)		Total (n = 49)	
	r	p	r	p	r	p	r	p
PW mean	0.80	0.001	0.95	0.001	0.96	0.001	0.87	0.001
A wave	0.92	0.004	0.98	0.001	0.95	0.001	0.90	0.001
LA size/PW mean	0.61	0.010	0.82	0.003	0.90	0.001	0.70	0.001
V slope	0.61	0.008	0.37	NS	−0.27	NS	0.47	0.001
MR index	0.55	0.020	0.48	NS	−0.08	NS	0.58	0.001
LA size	0.25	NS	0.16	NS	0.29	NS	0.52	0.001
LVEDP	0.54	0.020	0.73	0.010	0.63	0.001	0.45	0.001
Ejection fraction	0.24	NS	−0.21	NS	−0.55	0.007	−0.12	NS

Abbreviations as in Table I.

patients with a large V wave with and without mitral regurgitation [$F(1,25) = 10.682$, $p < 0.01$]. Using a slope of 90 mm/s as a cutoff point for the presence (slope less than 90) or absence (slope greater than 90) of mitral regurgitation, 17% of patients with and 80% of patients without mitral regurgitation were diagnosed correctly. For the mitral regurgitation index, a cutoff point of 8 (greater than 8 = no mitral regurgitation, less than 8 = mitral regurgitation) had a sensitivity of 82% and a specificity of 70%. The V/PW mean ratio did not allow a useful separation between patients with and those without mitral regurgitation, which was expected because both groups have a similar mean V/PW ratio (Table I).

Large V wave in absence of mitral regurgitation: To evaluate the factors that may participate in the pathogenesis of a large V wave in the absence of mitral regurgitation, comparisons were made between groups II and III (all without mitral regurgitation). The correlations between the magnitude of the V wave (mm Hg) and all other echocardiographic and hemodynamic variables were determined. Table III summarizes the variables that have a statistically significant correlation. The statistically significant different variables were the height of the A and V waves, the mitral regurgitation index, the ratio V wave/pulmonary wedge mean pressure, the slope of ascent of the V wave, mean pulmonary wedge pressure, and the size of the left atrium. Both groups had similar age, sex, aortic systolic and diastolic pressures, cardiac index, ejection fraction, echographic left ventricular dimensions (septum, posterior wall, and internal diameter), left ventricular mass, peak stress, and the ratio of left atrial size to pulmonary wedge mean pressure.

Discussion

Previous studies: The V wave on the venous pulse was first described by McKenzie[15] in1902. It represents passive filling of the left atrium during ventricular systole, peaking just before the mitral valve opens. Normally, the V wave is slightly larger than the A wave in the left atrium; although slightly damped and phase delayed, the V wave as recorded from the pulmonary wedge position is an accurate representation of the V wave in the left atrium.[16,17] A large V wave has been considered typical of mitral regurgitation,[18,19] and a number of indexes have been reported to correlate the size and morphology of the V wave with the severity of mitral regurgitation. Kent et al.[20] suggested that V waves 5 mm Hg or greater than the C wave indicate mitral regurgitation, but Wells[21] proved this inaccurate; although most patients with severe mitral regurgitation

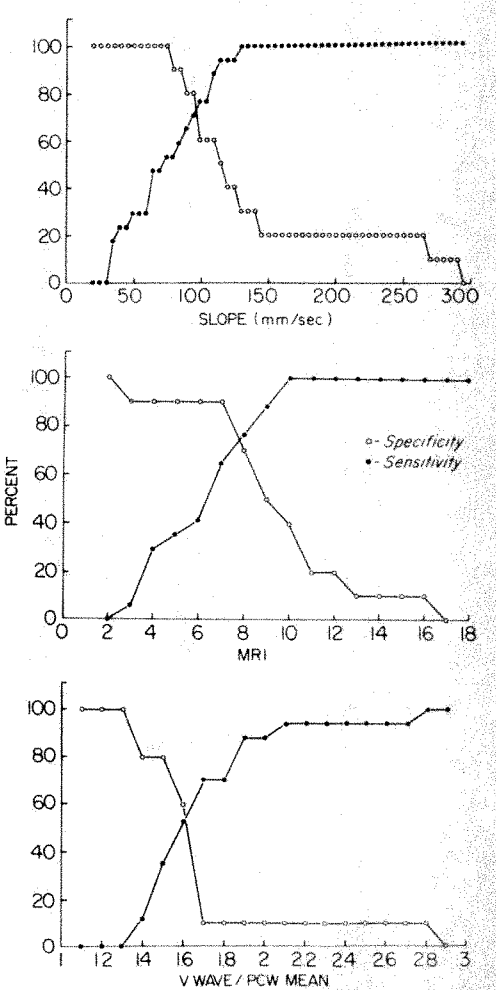

FIGURE 1. Sensitivity and specificity curves for the entire study population. The **vertical axis** shows the percent of sensitivity and specificity. The **horizontal axis** shows the slope of ascent of the V wave (**top**), the mitral regurgitation index (**middle**), and the V/pulmonary wedge mean pressure (PCW) ratio (**bottom**).

fit the rule, many patients with mild or absent mitral regurgitation also had a V-C wave difference greater than 5 mm Hg. Connolly and Wood[22] studied the ratio of peak V/mean pulmonary wedge pressure and found it a good index to separate patients with mitral regurgitation from those with mitral stenosis or from normal patients, but only if the mean pulmonary wedge pressure was 20 mm Hg or greater. When this pressure was lower, they exercised the patients to elevate the wedge pressure and were able to use the index reliably. These results have also been disputed.[23]

Libanoff and Rodbard[8] also tried to differentiate mitral stenosis from mitral regurgitation by creating a mitral stenosis index and a mitral regurgitation index. The mitral regurgitation index measures the slope of the rise of the V wave and divides it by the cardiac index because the more severe the mitral regurgitation, the greater the reduction in forward cardiac index. Using this index they were able to differentiate predominant mitral regurgitation from predominant mitral stenosis.

Formulas relating the rate of Y descent to the height of the V wave[24] or to mean left atrial pressure[25] are concerned more with the severity of obstruction to atrial emptying than with the severity of mitral regurgitation.

Variables relating a large V wave to the presence or absence of mitral regurgitation: We have observed that a large V wave in the pulmonary wedge pressure tracing often is not associated with mitral regurgitation.[7] In this study we confirmed that observation and found that 37% of patients with large V waves have no clinical or angiographic evidence of mitral incompetence. These patients had a wide variety of other cardiac diseases. When analyzing all patients with large V waves, we found that the only significant differences between those with mitral regurgitation (group I) and those without it (group II) were in the slope of ascent of the V wave (group I: 74.3; group II: 141.9; $p = 0.021$) and in the mitral regurgitation index of Libanoff and Rodbard[8] (group I: 6.01; group II: 9.45; $p = 0.005$). The absolute size of the V wave as well as its size relative to the mean pulmonary wedge pressure were not significantly different in the 2 groups (Tables I and II). The best discriminant value for slope of ascent was 90 mm/s, for mitral regurgitation index 8, and for the V/PW ratio 1.6. The slope had the best predictive value for mitral regurgitation with a sensitivity of 70% and a specificity of 80%. However, none of the variables allowed us to confirm or discard the presence or absence of mitral regurgitation with 100% accuracy. The size of the V wave and the ratio V/PW mean were similar in groups I and II (38.5 ± 11 versus 37.5 ± 11 mm Hg and 1.67 ± 0.3 versus 1.69 ± 0.4, respectively, p = NS) and were not helpful in predicting the presence or absence of mitral regurgitation.

Mechanism of a large V wave in the absence of mitral regurgitation: Looking for an explanation of why among patients without mitral regurgitation, some have a large V wave and some do not, we compared patients from group II (large V wave, no mitral regurgitation) with patients in group III (no mitral regurgitation, no large V wave) and found that patients in group II had a significantly higher mean pulmonary wedge pressure, a left atrium of larger size, a greater mitral regurgitation index, a faster slope of ascent, and a larger A wave than those in group III. These findings can be explained by considering the characteristic compliance of the left atrium and pulmonary veins as well as the other factors that determine the height of the V wave. The volume/pressure relation of the left atrium and pulmonary veins is not linear and can be depicted by a curve (Fig. 2) whereby small changes in volume produce little change in pressure when the left atrial or pulmonary wedge pressure is low, but a small change in volume is associated with a large change in pressure at the high pressure end of the curve. This compliance curve is characteristic of venous tissue,[26–29] and varies widely from patient to patient.[27,30] In our study, patients with a large V wave and no mitral regurgitation had an abnormally elevated pulmonary wedge pressure (mean 23.5 ± 8 mm Hg), so they were probably at the upper end of the compliance curve of the pulmonary venous left atrial system, resulting in a large V wave during atrial filling. In fact, the size of the V wave had a significant correlation with the magnitude of the pulmonary wedge mean pressure in all 3 groups (Table III). The large V wave in group II occurred despite a larger left atrial size than that in group III. This finding indicates that a high distending pressure may be present in a left atrium of any size[31,32] depending on the characteristic compliance of the left atrium and pulmonary venous system. The size of the left atrium may be related more to the duration and nature of the pathologic process (that is, rheumatic heart disease) than to the left atrial pressure.

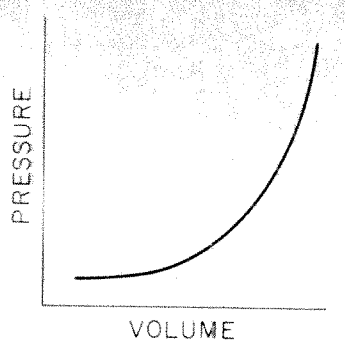

FIGURE 2. Compliance curve in the left atrium and pulmonary venous system. At the right end of the curve, small changes in volume are accompanied by large changes in pressure.

The slope of ascent of the V wave and the mitral regurgitation index were steeper (faster) in patients without mitral regurgitation than in those with mitral regurgitation (group II versus group I). Although this finding is unexpected, it could be explained as follows: patients without mitral regurgitation who had a high V wave (group II) are in such a steep portion of the pulmonary venous-left atrium compliance curve that the change in pressure occurs very rapidly as the atrial

volume increases toward the end of ventricular systole. However, in patients with mitral regurgitation the upstroke of the V wave begins earlier, with obliteration of the X descent[21] and a slower rate of rise toward its peak.

The size of the V wave is determined by a number of factors in addition to the compliance of the venous system[33–35]: (1) the initial volume of blood contained in the pulmonary venous-atrial system, (2) the rate of forward flow of blood to the left atrium, (3) the systemic arterial and left ventricular pressure, which is especially important in patients with mitral regurgitation in whom the amount of regurgitant volume varies in direct relation to the level of the afterload, and (4) the force of contraction of the left ventricular ring during ventricular systole. Considering the principal factors that determine the size of the V wave and the pressure in the pulmonary venous-left atrial system, we can explain why some patients without mitral regurgitation have a large V wave and also why some patients with severe mitral regurgitation may have normal left atrial pressure and a normal V wave.[36]

Clinical implications: As flow-directed catheters for hemodynamic monitoring have become widely available[37,38] and because the central venous pressure has been discarded as an appropriate index of left ventricular filling pressure in patients with acute myocardial infarction or other severe medical or surgical conditions,[3,4] an increasing number of patients undergo right heart catheterization during their stay in an intensive care unit.[1,2] The presence of a large V wave in the pulmonary wedge pressure is usually interpreted as representing mitral regurgitation,[5,6] and therapy may be modified accordingly. Awareness of the findings of our study, that is, that a large V wave may not be associated with mitral regurgitation, seems most important among physicians performing hemodynamic monitoring of patients in critical condition. The data in our study demonstrate that the size of the V wave or the mean pulmonary wedge pressure ratio is not useful in predicting the presence or absence of mitral regurgitation. An exception to this concept are patients with acute mitral regurgitation, known to have giant V waves.[39] Determining the slope of ascent of the V wave, a measurement not always possible in bedside hemodynamic monitoring, is a more sensitive and specific test in the diagnosis of mitral regurgitation. Our findings are also relevant in the interpretation of data obtained in the catheterization laboratory, especially in cases in which the diagnosis of mitral regurgitation is in question or in cases in which left ventriculography is not definite or diagnostic for the presence or absence of mitral regurgitation.

Limitations of the Study

Angiographic determination of mitral regurgitation: Selective angiography is the procedure of choice for evaluating the competence of the mitral valve.[40] As long as the ventricle is well opacified, any amount of mitral regurgitation will be detected. The problems with left ventriculography are creation of artifactual mitral regurgitation due to premature beats or catheter malposition and quantification of the mitral regurgitation.[41] These possible pitfalls of left ventriculography should not alter the conclusions and clinical implications of our study.

Study population: All patients in our study were referred for diagnostic cardiac catheterization and angiography. They may not be representative of the population undergoing right heart catheterization in intensive care units, in which case the proportion of patients with a large V wave and no mitral regurgitation may be different. Our analysis of the hemodynamic factors related to the high V wave should remain valid.

Pulmonary wedge pressure may not reflect exactly the changes in pressure occurring in the left atrium: A close relation between pulmonary wedge and left atrial pressure was demonstrated many years ago.[42,43] Minimal differences in peak, minimal, and mean pressure (averaging less than 1 mm Hg) are common,[44] but larger differences (pulmonary wedge pressure 35% higher than left atrial pressure) have been reported.[45] A phase delay in pulmonary wedge pressure is produced by the distance between the pulmonary vessel containing the wedge catheter and the left atrium. We previously demonstrated by simultaneous recording of pulmonary wedge and left atrial pressure (unpublished data) that some patients have a relative damping of the pulmonary wedge pressure tracing, especially in the slope of the Y descent; this damping effect does not suppress the cyclical changes in left atrial pressure, especially when the latter is elevated above normal.[46]

Direct left atrial pressure recording could have allowed better analysis of the morphology of the V wave and its relation to other hemodynamic variables. This remains to be studied. The major finding in our study, that is, that large V waves can occur in the absence of mitral regurgitation, should not be altered by these considerations.

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Pregnancy in Patients With a Porcine Valve Bioprosthesis

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Seven patients who became pregnant after valve replacement with a Hancock bioprosthesis were followed up during 8 pregnancies. Six had undergone isolated mitral valve replacement, and 1 had mitral and aortic valve replacement. Their age at the time of operation ranged from 14 to 31 years (average 24); delivery occurred 21 to 88 months (average 51.3) after valve replacement. All women were in sinus rhythm at the time of gestation, and administration of oral anticoagulants was avoided in all. No embolic episodes occurred either after operation or during pregnancy, labor, or puerperium. The only major complication during pregnancy was cardiac failure in 1 patient, associated with onset of atrial fibrillation.

Four women had vaginal delivery and 3 required cesarean section. All but 1 delivered a normal, healthy baby. One premature infant died soon after birth because of respiratory distress. No maternal or fetal hemorrhagic complications were observed.

One patient died 3 months after delivery in severe heart failure caused by diffuse calcification of both mitral and aortic xenografts. Another woman underwent successful reoperation soon after the second pregnancy because of calcific stenosis of the mitral porcine valve.

It is concluded that (1) bioprosthetic valves can be considered the most suitable devices employed in women of childbearing age because anticoagulants can be avoided, therefore eliminating the risks related to inappropriate administration of oral anticoagulants as well as the hazards associated with the potential teratogenic effect of coumarin drugs; and (2) pregnancy might favor calcification of porcine heterografts, leading to bioprosthetic failure. Until further data are available to support this suspicion, close clinical and echocardiographic follow-up study of these patients is recommended after pregnancy.

Pregnancy may be hazardous in patients with a mechanical prosthesis because administration of an oral anticoagulant may be harmful to the fetus whereas suspension of such treatment exposes the mother to an undue risk of embolic complications.[1-5] For this reason, the use of porcine bioprostheses is recommended in young women of childbearing age. However, little information is currently available on the clinical course of patients who become pregnant after heart valve replacement with a porcine xenograft. We present our experience in a series of 7 such patients.

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Methods

Patients: Seven women who had previously undergone cardiac valve replacement employing 1 or more glutaraldehyde-preserved Hancock bioprostheses (Hancock Laboratories Anaheim, California) subsequently became pregnant. Their ages ranged from 14 to 31 years at the time of operation (mean 24). Six received isolated mitral valve replacement and 1 received combined mitral and aortic valve replacement. Indications for surgery were rheumatic endocarditis in 6 and congenital mitral insufficiency in 1. All patients were maintained postoperatively on a regimen of digoxin, which was combined with diuretic therapy in 3. An oral anticoagulant (sodium warfarin) was administered in all until the third postoperative month and discontinued thereafter.

Pregnancy and labor: All patients were accurately followed up during pregnancy and hospitalized at least 3 weeks before the expected time of delivery. During labor and delivery, maternal and fetal heart rates, maternal blood pressure, and central venous pressure were continuously monitored.

TABLE I Summary of Clinical and Follow-Up Data

Case	Age (yr) at PVR	Operation	Prepartum NYHA Class and Rhythm	Interval From PVR to Delivery (mo)	Anticoagulation During Pregnancy	Other Medications During Pregnancy	Type of Delivery	Complications During Pregnancy	Follow-up Data
1	18	MVR	1, SR	72	None	Digoxin	Cesarean, at term	AF, 6th mo	Functional Class 3, AF, 11 yr 2 mo postoperatively
2	25	MVR	1, SR	88	None	Digoxin	Cesarean, at term	Threatened to abort, 11th wk	Functional Class 1, SR, 9 yr 10 mo postoperatively
3*	14	MVR	1, SR	48	None	Digoxin	Vaginal, at term	None	
			2, AF	84	Calcium heparin	Digoxin, diuretics	Vaginal, premature	Cardiac failure, AF, 7th mo	Reoperated for calcific stenosis of mitral bioprosthesis during puerperium; functional Class 1, AF, 1 yr after reoperation
4	24	MVR	1, SR	21	None	Digoxin	Vaginal, at term	None	Functional Class 2, SR, 8 yr postoperatively
5	31	MVR	1, SR	42	None	Digoxin	Vaginal, at term	None	Functional Class 1, SR, 6 yr 2 mo postoperatively
6	30	MVR	1, SR	33	None	Digoxin, dipyridamole	Cesarean, 8th mo	Threatened to abort, 11th wk	Functional Class 1, SR, 5 yr 9 mo postoperatively
7	28	AVR, MVR	2, SR	23	None	Digoxin, diuretics	Vaginal, at term	None	Died from cardiac failure 2 mo after delivery; at necropsy, calcific stenosis of both bioprostheses

* This patient had 2 pregnancies.
AF = atrial fibrillation; AVR = aortic valve replacement; MVR = mitral valve replacement; NYHA = New York Heart Association functional class; PVR = prosthetic valve replacement; SR = sinus rhythm.

During the first week of the puerperium, electrocardiograms were taken frequently. All patients received prophylactic wide-spectrum antibiotics during labor and for the first 5 postpartum days.

Results

Clinical data (Table I): The 7 women were followed up during 8 pregnancies, at which time their ages ranged from 18 to 35 years (mean 28); the interval between valve replacement and delivery averaged 51.3 months (minimum 21, maximum 88).

All women were in sinus rhythm at the onset of pregnancy; 6 were in functional class I (New York Heart Association criteria) and 1 was in class II. In 1 patient (Case 1) atrial fibrillation developed during the 6th month of gestation; another (Case 3), who was in sinus rhythm and in class I at the time of her first pregnancy, changed to class II when she became pregnant for the second time; during the seventh month of her second gestation atrial fibrillation developed.

Medications administered during pregnancy included digoxin in all cases, occasionally associated with diuretics, and antiplatelet drugs in 1. No anticoagulants were given, except in 1 patient (Case 3) who received low dose calcium heparin subcutaneously starting at the 32nd week of her second pregnancy, when she was hospitalized because of the onset of cardiac failure and atrial fibrillation.

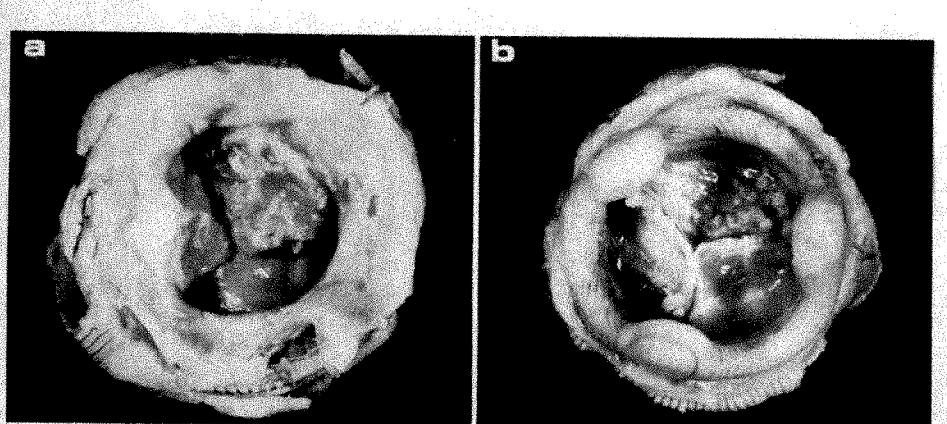

FIGURE 1. Case 3. Gross appearance of the explanted mitral porcine bioprosthesis. The device was recovered at reoperation performed for severe prosthetic stenosis. **a,** atrial view showing fibrocalcific tissue overgrowth partly covering the surface of the cusps. **b,** ventricular aspect of the same device demonstrating the calcific infiltration of cusps and commissures, with severe stiffness and stenosis of the xenograft.

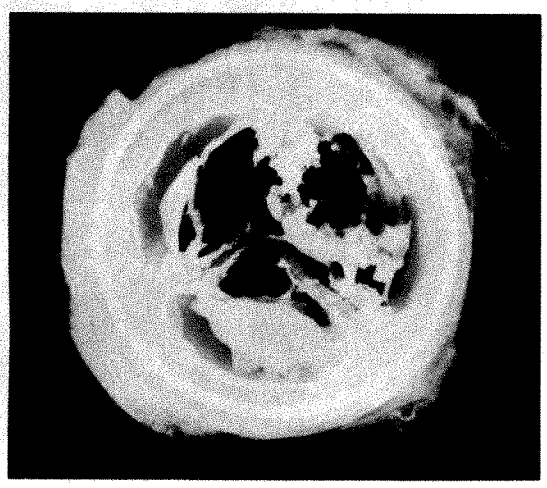

FIGURE 2. Case 3. X-ray examination of the same explant showing coarse calcific deposits in all cusps and commissures.

All pregnancies but 1 were carried out successfully. Four patients had a vaginal delivery; 3 of them gave birth at term to a healthy baby. One (Case 3) delivered for the 1st time a normal baby at term, whereas at the eighth month of her second pregnancy she delivered a premature infant with severe respiratory distress who died shortly thereafter.

Three women had a cesarean delivery based on obstetric indications, performed under general anesthesia. No significant variations in the fetal heart rate and no excessive blood loss occurred in any patient, regardless of the type of delivery.

Complications during pregnancy, labor, and puerperium: In 2 patients (Cases 2 and 6) the possibility of a spontaneous abortion arose around the 11th week of gestation; both were successfully managed. One patient (Case 3) had evidence of congestive heart failure during the second pregnancy, coincident with the onset of atrial fibrillation; she was managed with digitalis, diuretics, and calcium heparin.

Labor was well tolerated in all cases. Complications during puerperium were observed only in Patient 3. The persistence of heart failure in this case, despite vigorous medical treatment, prompted a hemodynamic investigation which revealed severe stenosis of the mitral valve bioprosthesis. This patient was successfully reoperated on shortly after delivery; at surgery the mitral porcine valve appeared grossly calcified and stenotic and was replaced with a mechanical prosthesis (Fig. 1). Both x-ray (Fig. 2) and ultrastructural (Fig. 3) investigations confirmed the presence of calcific deposits in the cusps tissue. No systemic embolic episodes occurred during pregnancy, labor, or puerperium.

Late results and follow-up: In 1 patient (Case 7) severe heart failure developed 3 months after delivery. She was erroneously considered at another institution to have cardiomyopathy and eventually died despite medical treatment. Necropsy revealed that both the aortic and mitral xenografts were highly calcified and stenotic, with thrombosis of the cusp sinuses; death was therefore ascribed to bioprosthesis dysfunction.

FIGURE 3. Case 3. Transmission electron micrograph of 1 cusp of the same device. Within the cytoplasm of a native pig cell calcification is present, resulting from the concentric deposition of hydroxyapatite crystals. The collagen bundles, surrounded by interstitial edema, are still fairly preserved. (Uranyl acetate and lead cytrate; original magnification ×18,000, reduced 44%.)

Five patients are currently alive approximately 6 to 11 years after operation and 1 to 6 years after pregnancy; the sole woman who was reoperated on is asymptomatic 1 year after prosthetic valve replacement. Four patients are still in sinus rhythm and 2 in atrial fibrillation; only 1 of the latter is receiving an oral anticoagulant. Four women are in functional class I, 1 is in class II, and 1 in class III. This patient (Case 1) is the only one to have undergone control cardiac catheterization, which demonstrated stenosis of the mitral valve bioprosthesis; she is presently awaiting reoperation. In 2 other cases an echocardiographic investigation recently performed showed that the porcine valve appears to function properly in both patients. Finally, in 1 case (Patient 4) dysfunction of the mitral xenograft is suspected on clinical grounds because of an apical systolic regurgitant murmur.

Discussion

Advantages of bioprosthesis valve in pregnant women: Women of childbearing age with valvular heart disease may represent a difficult problem for the sur-

geon to whom they are referred for prosthetic valve replacement. Various groups have reported their experience with mechanical prostheses in pregnant patients and the numerous complications related to the use of anticoagulants in such cases.[1–4,6–9] Oral anticoagulants of the warfarin type may be dangerous for the fetus because they cross the placental barrier and may cause fetal hemorrhage and malformation.[5,10–13] Moreover, the mother may be exposed to the risk related to either excessive or reduced anticoagulation, which may threaten both her life and the survival of the fetus.[1–3] As a consequence, gestation in women with a mechanical prosthesis, although feasible, is very hazardous; therefore, extreme care in the use of anticoagulants as well as accurate cardiovascular management is considered a prerequisite of successful pregnancy in such patients.[7]

Porcine bioprostheses have been advocated in young women of childbearing age,[2] because problems and hazards related to anticoagulant treatment, which may be avoided in most patients receiving such devices, are considerably reduced. However, little is known about the course of pregnancy in patients with a porcine heterograft. Our experience underlines that women who become pregnant after prosthetic valve replacement with a porcine bioprosthesis may successfully carry on their pregnancy without significant prosthesis-related complications.

The hypercoagulability state occurring during pregnancy[14,15] usually increases the need for anticoagulant therapy in patients with an artificial valve. In the present series, no oral anticoagulants were administered throughout pregnancy, labor, or puerperium, and no systemic embolic episodes were noted. This good result may probably have been favored by the fact that all women were in sinus rhythm; nevertheless, the absence of embolic complications is relevant.

The circulatory overload which occurs in pregnancy may be poorly tolerated by women with obstruction of the left atrial outflow, resulting in severe pulmonary congestion.[14–16] We have observed this complication only once; indeed, this patient required reoperation shortly after delivery because of severe stenosis of a mitral bioprosthesis. The dysfunction of the xenograft likely contributed to the onset of congestive heart failure.

Porcine valve calcification: relation to pregnancy: We were highly impressed by the severe calcification of the porcine heterograft implanted in 2 patients of this series. One underwent successful reoperation whereas the second died from heart failure before reoperation could be performed. This experience led us to suspect that pregnancy might favor calcification of the porcine xenograft, although the possible mechanisms remain unclear. The level of serum calcium is usually normal or slightly depressed during pregnancy[17]; however, an increased turnover of calcium could occur in the mother in order to fulfill the requirements of the growing fetal skeleton. Calcium, most likely derived from the mother's bones, could partly be deposited on foreign biologic tissue, such as the porcine valve cusps. One must consider, however, that in 1 of our patients (Case 3), dysfunction of the mitral bioprosthesis became apparent after her second pregnancy and that the same patient was an adolescent at the time of valve replacement; indeed, calcification of porcine heterografts implanted in young subjects has been reported repeatedly.[18–20]

Implications: Further data are needed to confirm whether a relation exists between pregnancy and calcification of porcine valves. In the meantime, a closer cardiologic follow-up study of such patients, possibly associated with periodic echocardiographic evaluation, appears advisable after delivery in order to detect early signs of bioprosthetic dysfunction. Our current policy in dealing with young women who need a prosthetic valve and who desire to carry on a pregnancy after valve replacement is to explain to them that having the valve replaced with a biologic prosthesis is the simplest and safest way to have a child, because with such a device complications during pregnancy are minimized. However, reoperation for bioprosthetic failure might be needed earlier than expected.

According to our results, pregnancy in patients with a porcine bioprosthesis is well tolerated and successfully carried out in most cases. The absence of embolic episodes in this series, despite the lack of anticoagulant treatment and the hypercoagulability state of pregnancy, suggests that bioprostheses are currently the most suitable devices for use in women of childbearing age.

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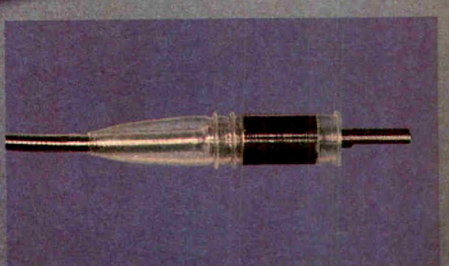

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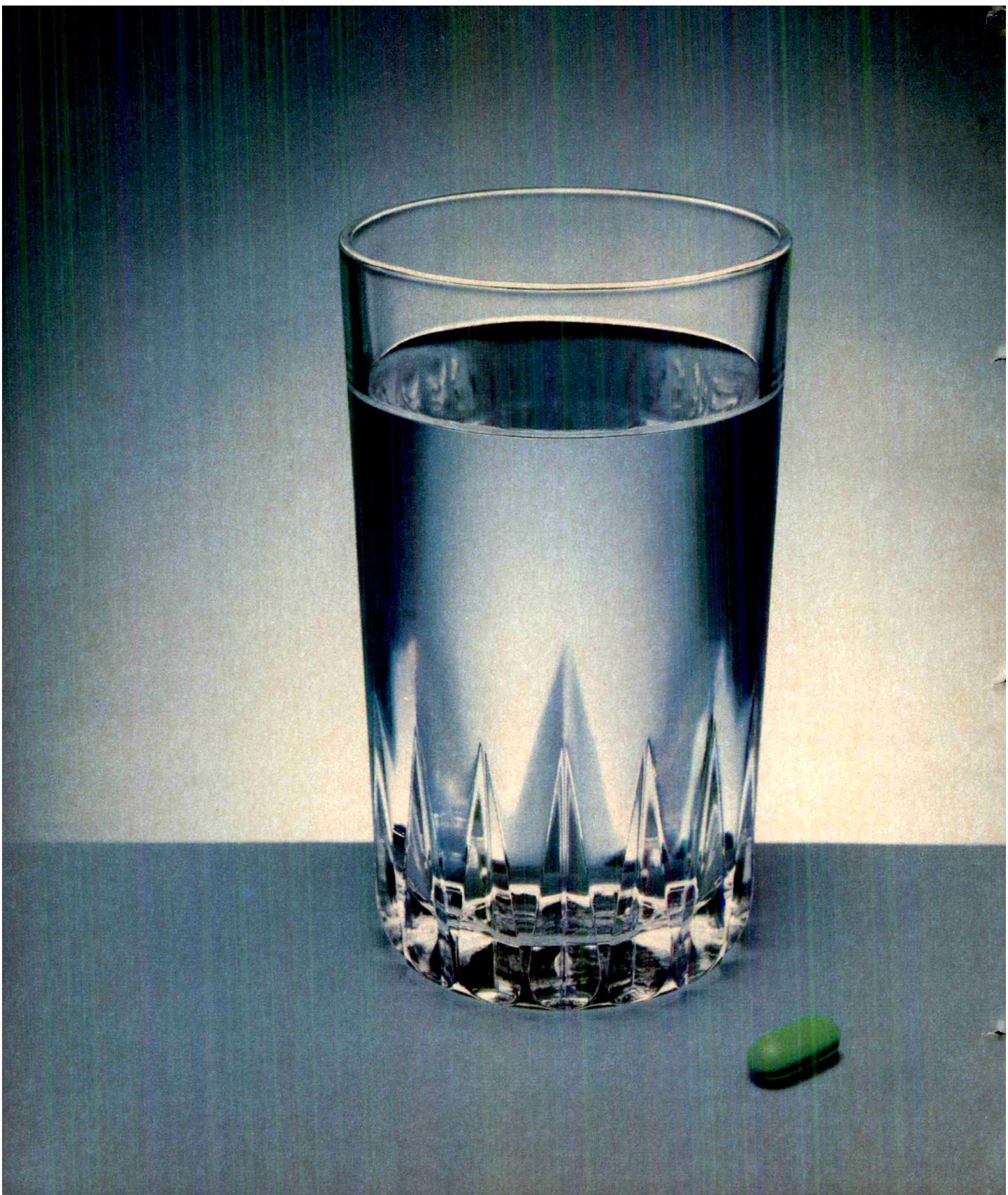

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3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon Cl™-10 mEq (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient years. Kaon Cl-10 mEq should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:
Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 ml.
Correction of acidosis, if present, with intravenous sodium bicarbonate.
Use of exchange resins, hemodialysis, or peritoneal dialysis.

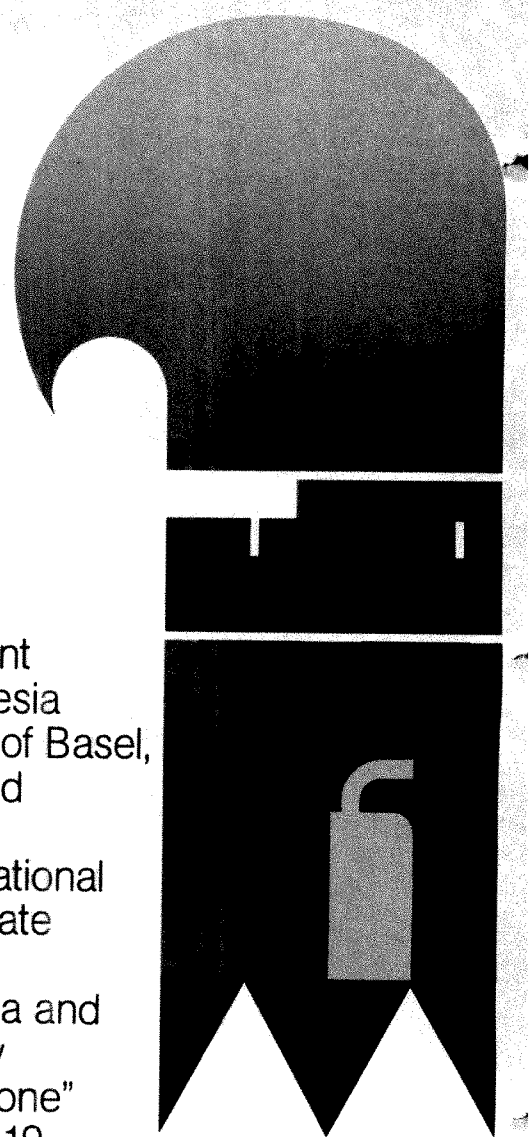
In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

Caution: Federal law prohibits dispensing without prescription.

How Supplied: Bottles of 100 and 500; Stat-Pak® (Unit-Dose) box of 100.

Adria

Adria Laboratories Inc., Columbus, Ohio 43215 088121



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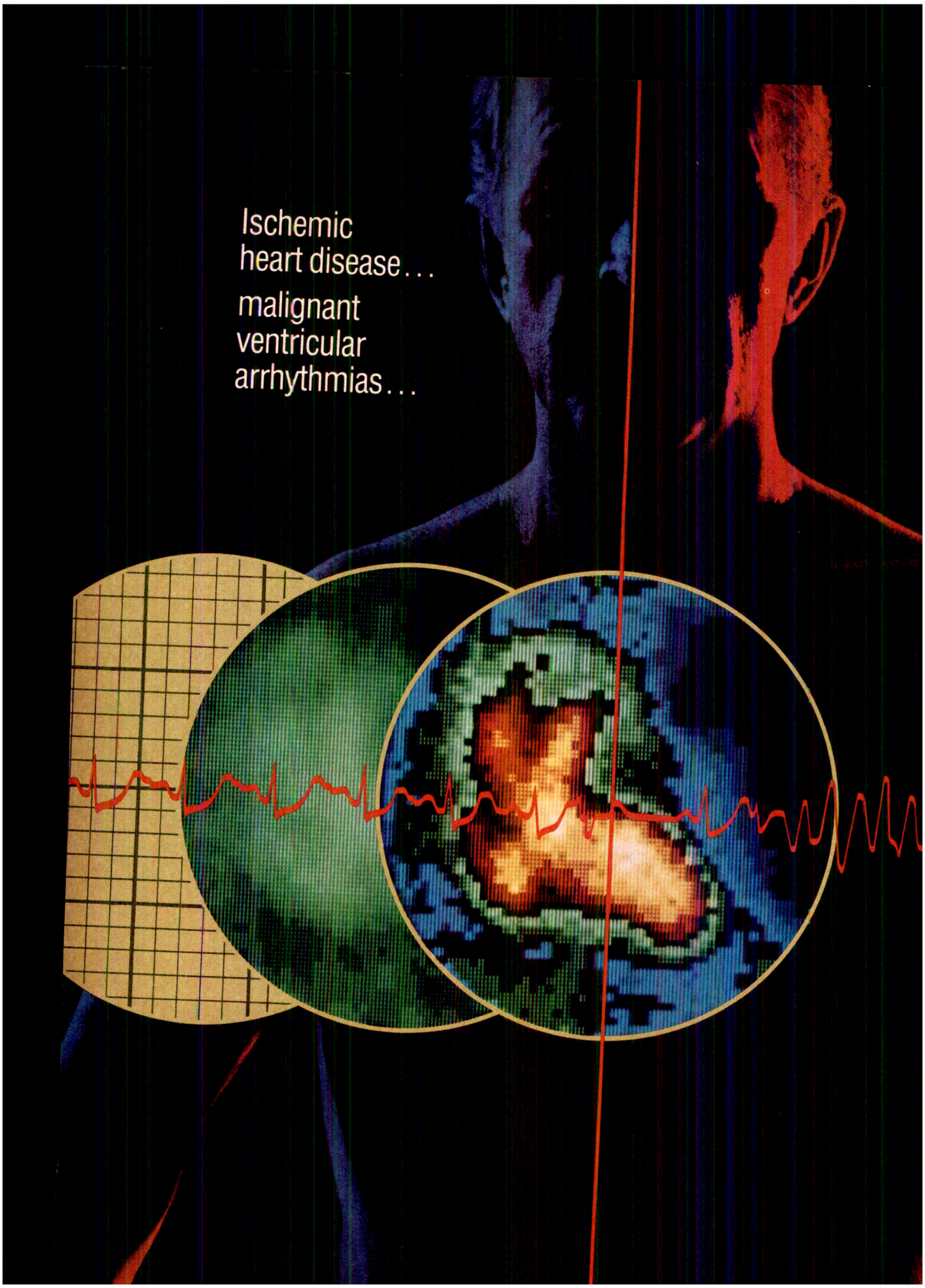
Ischemic
heart disease...
malignant
ventricular
arrhythmias...

ZEROING IN ON THE CANDIDATE AT RISK

Frequent and complex forms of PVCs sharply increase the risk of sudden cardiac death (SCD) in patients with ischemic heart disease, especially in the presence of left ventricular dysfunction.[1,2]

To reduce the risk of potentially fatal arrhythmias in such patients

QUINAGLUTE® 324 mg DURA-TABS®

(quinidine gluconate)

- If initially tolerated, can usually be taken successfully over long periods.[3]
- Demonstrated by programmed ventricular stimulation to be effective in accepted "standard" doses.[4]
- BID or TID dosage helps improve compliance while providing 24-hour antiarrhythmic activity.
- "As a rule, GI toxicity associated with quinidine gluconate is less frequent and less severe than that associated with quinidine sulfate."[5]

References: **1.** Lown B, Podrid PJ, Graboys TB, et al: *Curr Probl Cardiol* 4:13-14, 1980. **2.** Schulze RA Jr, Strauss HW, Pitt B: *Am J Med* 62:192-199, 1977. **3.** Pine MB, Aronow WS: *Ration Drug Ther* 14:1-5, 1980. **4.** Kastor JA, Horowitz LN, Harken AH, et al: *N Engl J Med* 304: 1004-1020, 1981. **5.** Podrid PJ: *Patient Care* 15:100-132, 1981.

Please turn page for brief summary of prescribing information.

BERLEX Laboratories, Inc., Cedar Knolls, New Jersey 07927

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QUINAGLUTE® (quinidine gluconate) DURA-TABS®
INDICATIONS AND USAGE: Quinaglute (quinidine gluconate) Dura-Tabs are indicated in the prevention and/or treatment of:
1. Ventricular arrhythmias: Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock).
2. Junctional (nodal) arrhythmias: A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).
CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.
WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.
2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered.
3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.
4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.
5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity.
7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.
8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.
PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.
Drug Interactions:

Drug	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.
Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.
Nursing Mothers: Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.
Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.
ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea.
Less frequently encountered adverse reactions:
Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.
Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.
Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.
Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.
Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.
See package insert for full information.
BERLEX Laboratories, Inc., Cedar Knolls, New Jersey 07927

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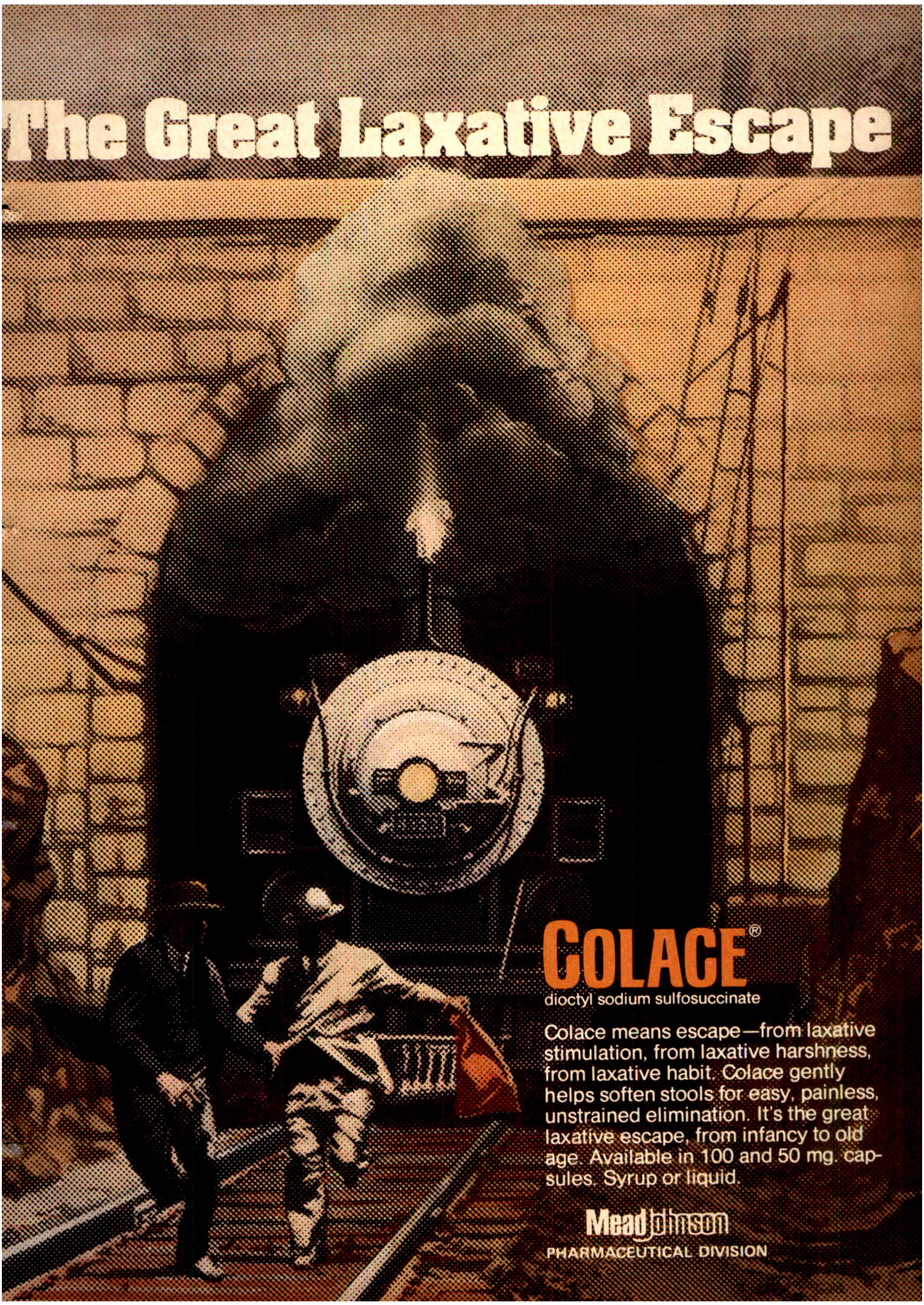
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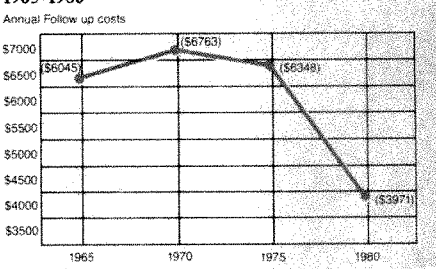
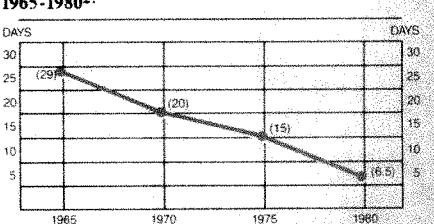


1. Ref. cit. "A Fifteen Year Study of Cardiac Pacing Costs", C. Langer, A. Lopman, S. Furman, D. Escher. *PACE*, May-June, 1981.

DECLINING NUMBER OF HOSPITAL DAYS PER PACEMAKER PATIENT 1965-1980[2].



2. Ref. cit. "A Fifteen Year Study of Cardiac Pacing Costs", C. Langer, A. Lopman, S. Furman, D. Escher. *PACE*, May-June, 1981.

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Intended Uses

Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses). An atrial pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation disorders but with intact, functioning A-V conduction systems. Cardiac pacing using an implantable A-V sequential pulse generator is for long-term therapeutic control of heart rate in patients where restoration of A-V synchrony is indicated to improve cardiac output or to protect against arrhythmias related to sequence of cardiac impulse propagation.

Contraindications

There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.

Warnings

Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. See the specific precautions and warnings in the technical manuals included with the pulse generator.

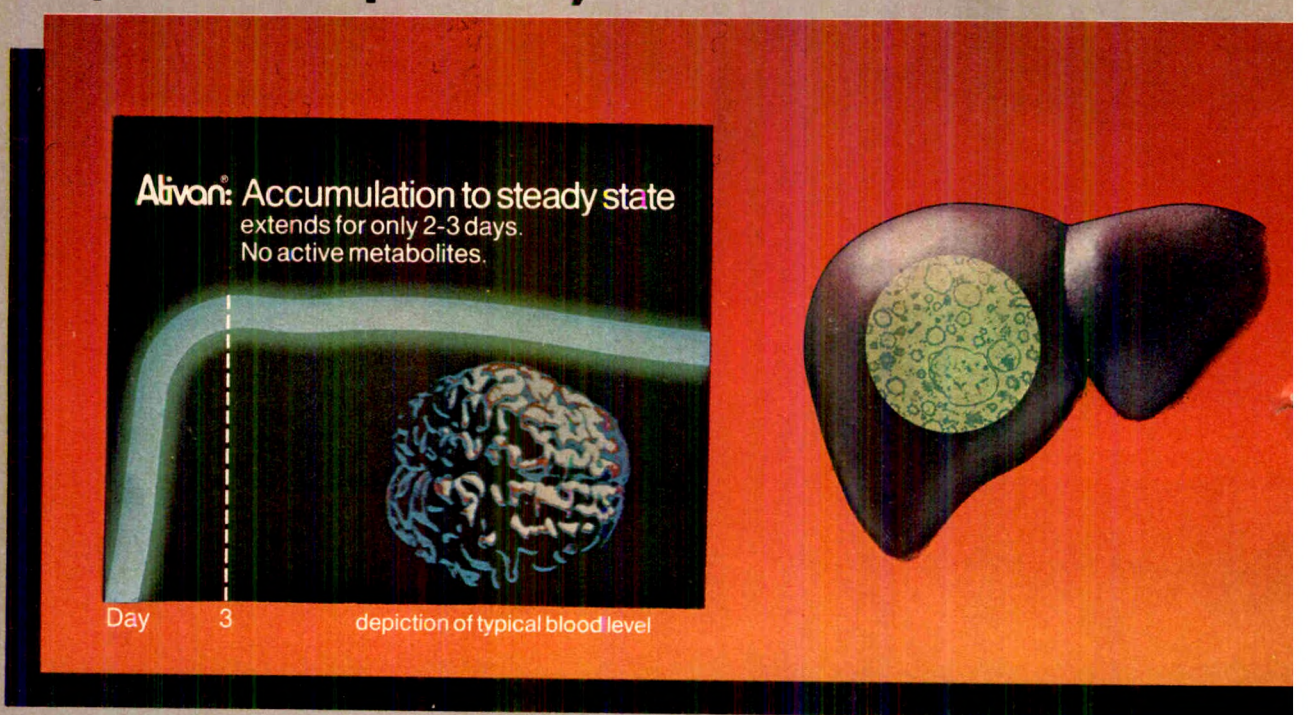
Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

Ativan®: Agent
(lorazepam)



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In contrast to long-acting benzodiazepines, Ativan has a short, 12-hour half-life, and no active metabolites. In multiple-dose therapy, Ativan accumulates for only 2 to 3 days before reaching steady state; the long-acting benzodiazepines—diazepam CIV, chlordiazepoxide CIV, clorazepate CIV and prazepam CIV—with their active metabolites accumulate for as long as 20 days before reaching steady state. Cumulative sedative effects are seldom a problem with Ativan.[1]

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1. Shader RI, Greenblatt DJ, Ciraulo DA: Psychiatric Annals *11*:16-20, 1981.
2. Klotz U, Reimann I: N Engl J Med *302*:1012-1014, 1980.
3. Desmond PV, Patwardhan RV, Schenker S, et al: Ann Intern Med 93:266-268, 1980.
4. Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology *79*:912-916, 1980.
5. Sellers EM, Naranjo CA, Peachey JE: N Engl J Med *305*:1255-1262, 1981.
6. Ruffalo RL, Thompson JF, Segal JL: South Med J *74*:1075-1078, 1981.

*All benzodiazepines produce additive effects when given with CNS depressants such as barbiturates or alcohol.

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# of Change

it gives you greater control of therapy

The short half-life of Ativan® (lorazepam) facilitates more rapid response to dosage adjustments, allowing you to titrate therapy to patients' changing needs. Also, once you decide to discontinue Ativan, it will be out of your patient's system 4 days after the final dose—in contrast to long-acting benzodiazepines and their active metabolites which take as much as 2 weeks to be totally eliminated.

Ativan®
for (lorazepam) IV
Anxiety

Wyeth Laboratories
Philadelphia, PA 19101

See important information on following page.

Brief Summary of Prescribing Information

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan®
for (lorazepam) ℞
Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

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Electrophysiologic Drug Testing in Patients With Malignant Ventricular Arrhythmias: Importance of Stimulation At More Than One Ventricular Site

FRED MORADY, MD, DAVID HESS, MD, and MELVIN M. SCHEINMAN, MD

Sixty-four patients with symptomatic ventricular tachycardia or ventricular fibrillation underwent right ventricular apical programmed stimulation and had no inducible ventricular tachycardia during drug testing. Thirty patients (Group I) did not undergo left ventricular stimulation. Left ventricular stimulation in 38 drug trials induced no ventricular tachycardia in 50% (Group IIA), nonsustained ventricular tachycardia in 26% (Group IIB), and sustained ventricular tachycardia in 24% (Group IIC).

Patients in Groups I, IIA, and IIB received chronic antiarrhythmic drug therapy based on the results of electrophysiologic drug testing. Patients in Group IIC underwent further drug testing until sustained ventricular tachycardia was no longer inducible and were then entered into Group IIA or IIB; 4 patients in whom the induction of sustained ventricular tachycardia could not be suppressed by any drug regimen tested were excluded from long-term follow-up. The duration of follow-up (mean ± standard deviation) was 15.8 ± 11.5 months in Group I, 13.6 ± 3.7 months in Group IIA, and 12.1 ± 4.9 months in Group IIB. Recurrence rates of symptomatic ventricular tachycardia or sudden death were 27% in Group I, 0% in Group IIA, and 20% in Group IIB ($p < 0.02$ for Group IIA versus Group I and $p > 0.05$ versus Group IIB).

If only right ventricular apical stimulation is performed during electrophysiologic drug testing in patients with malignant ventricular arrhythmias, approximately 50% of drug trials may be incorrectly judged as suppressing the induction of ventricular tachycardia. Drug therapy that suppresses ventricular tachycardia induction with both right and left ventricular programmed stimulation results in a significantly better clinical response than therapy based on the results of only right ventricular apical stimulation.

Programmed ventricular stimulation has been demonstrated to result in the induction of ventricular tachycardia (VT) in 80 to 90% of patients who have had recurrent VT.[1-4] Furthermore, drug testing during programmed ventricular stimulation has been shown useful in predicting the long-term efficacy and inefficacy of antiarrhythmic drugs in preventing recurrent malignant ventricular arrhythmias.[1,3,5-7] Nevertheless, despite long-term treatment with drugs demonstrated to prevent the laboratory induction of VT, up to 32% of patients have been reported to have recurrence of VT over an 18 month follow-up period.[6]

Previous studies[1-4,8] of patients with documented VT revealed that programmed stimulation at multiple right ventricular sites or with multiple pacing rates, or both, results in the induction of VT in approximately 85 to 90% of patients. We found similar results in a consecutive series of 40 patients with spontaneous VT using a single right ventricular site (apex) and a single basic drive rate (500 ms) and triple extrastimuli. Thirty-five of these 40 patients (88%) had inducible VT. The proximity of the stimulation site to a potential reentry circuit is an important factor in the induction of a reentrant arrhythmia.[9,10] Because most adult patients with recurrent VT have coronary artery disease and VT that originates in the left ventricle,[11] it is possible that during drug testing some patients might have VT that

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can be induced with left but not right ventricular stimulation. If so, then programmed stimulation of the right ventricular apex alone might be an inadequate test of drug efficacy in suppressing VT induction.

Because our pilot studies showed that stimulation of the right ventricular apex with 3 extrastimuli induced VT in a similar percentage of patients as did more aggressive right ventricular stimulation protocols, we chose to assess the value of left ventricular programmed stimulation during drug testing in patients with malignant ventricular arrhythmias. Two main questions have been addressed with regard to electrophysiologic drug testing: (1) In patients in whom VT cannot be induced with right ventricular apical stimulation, how often will left ventricular programmed stimulation result in VT induction? (2) Is drug testing based on programmed stimulation of more than 1 ventricular site a better predictor of long-term clinical response than drug testing based on right ventricular apical stimulation alone?

Methods

Sixty-four patients with symptomatic VT or ventricular fibrillation (VF) form the basis of this report. In 40 patients, VT was documented in association with symptoms of syncope, presyncope, or palpitations either with a 24 hour ambulatory electrocardiographic recording or by an electrocardiogram obtained in the hospital or by paramedics. In 24 patients who had cardiac arrest, VF was documented before direct-current cardioversion. Patients with evidence of myocardial infarction within 4 weeks of the most recent episode of VT or VF were excluded as were patients with VT or VF due to metabolic disturbances such as severe hypokalemia. In addition, patients with the long Q-T syndrome were excluded based on a previous study demonstrating that programmed ventricular stimulation is of limited value in patients with this syndrome (Morady F et al., unpublished observations). Left ventricular ejection fraction was assessed either by left ventricular angiography at the time of cardiac catheterization or with a technetium-99m radionuclide angiogram.

Thirty patients (Group I) underwent only right ventricular apical programmed stimulation during drug testing and were found to have no inducible VT. Twenty-six of these patients were studied before initiation of a left ventricular stimulation protocol in our laboratory in January 1980. In the remaining 4 patients, left ventricular stimulation was not performed either because of a prosthetic aortic valve or marked tortuosity of the aorta or iliac arteries, preventing the retrograde passage of a electrode catheter across the aortic valve.

Thirty-four patients (Group II) who had no inducible VT with right ventricular apical stimulation during drug testing then underwent left ventricular programmed stimulation during the same study.

Electrophysiology study protocol: After obtaining informed consent, ventricular stimulation studies were performed in the fasting, unsedated state. A quadripolar electrode catheter was inserted percutaneously through a femoral vein and positioned against the apex of the right ventricle. A second catheter was positioned across the tricuspid valve for recording the His bundle electrogram. A short polyethylene catheter was inserted into a femoral artery for monitoring arterial blood pressure. For left ventricular stimulation, a bipolar electrode catheter was inserted percutaneously into a femoral artery and positioned against the apex of the left ventricle. Patients underwent systemic heparinization during left ventricular stimulation. Electrocardiographic leads V_1, I, and III and intracardiac electrograms were recorded using a VR-12 Electronics for Medicine recorder. Ventricular stimulation was performed with pulses 2 ms in duration, delivered at a constant current of 2 to 3 times the diastolic threshold by a programmable stimulator (Bloom).

The following ventricular stimulation protocol was used in all patients. Ventricular drive was instituted at a cycle length (S_1-S_1) of 500 ms and a single extrastimulus (S_2) was inserted 450 ms after the last driven complex and moved progressively closer to S_1, by 10 ms decrements, until the ventricular effective refractory period (VERP) was reached. The VERP was defined as the longest S_1-S_2 interval that did not evoke a ventricular response. If sustained VT was not induced, S_2 was positioned 30 ms outside the VERP and a second extrastimulus (S_3) was inserted and moved progressively closer to S_2 until ventricular refractoriness was reached. The S_3 was positioned 30 ms outside the point of refractoriness and a third extrastimulus (S_4) was then inserted and moved in by 10 ms decrements. If VT was not induced, S_2 and S_3 were moved progressively closer to S_1 and diastole was again scanned with S_4. Short bursts of overdrive pacing were then performed at cycle lengths of 600 to 300 ms. The same stimulation protocol was performed in both the right and left ventricles.

Sustained VT was defined as VT at least 30 seconds in duration or requiring direct-current cardioversion or overdrive pacing for termination. Nonsustained VT was defined as VT of 6 beats to 30 seconds in duration.

Drug testing protocol: In Group I, 26 of 30 patients underwent their initial study while being treated with 1 or more antiarrhythmic drugs. In 15 of the 30 patients, VT was induced during the initial drug trial, and further drug testing was performed until VT could no longer be induced with right ventricular apical stimulation.

In Group II, 20 of 34 patients underwent initial study while receiving antiarrhythmic drug therapy. Ventricular tachycardia was induced with right ventricular programmed stimulation during the initial study in 26 patients. These patients underwent further drug testing until VT could no longer be induced with right ventricular stimulation, and then they underwent left ventricular stimulation. Antiarrhythmic drugs were administered at the time of initial study in an attempt to prevent VT induction and minimize the need for direct-current cardioversion.

Drugs were tested based on each patient's history of drug intolerance and previous clinical response. The following oral agents were tested during the last 1 to 2 hours of the dosing interval, after administration of a sufficient number of doses to attain a steady-state serum drug level: procainamide, 3 to 8 g/day; quinidine, 1.2 to 1.6 g/day; disopyramide, 400 to 600 mg/day; propranolol, 160 to 480 mg/day; tocainide, 0.8 to 1.2 g/day; and dilantin, 300 mg/day. Because of its extended half-life, amiodarone, 600 to 800 mg/day, was tested 2 to 3 months after initiation of therapy. The following drugs were tested acutely in the laboratory after intravenous administration: procainamide, 750 to 1,500 mg; propranolol, 0.15 mg/kg; lidocaine, loading dose of 225 mg over 20 minutes, concomitant with a 2 mg/min continuous infusion.

Serum drug levels (procainamide, quinidine, propranolol, dilantin, or tocainide but not disopyramide, nadolol, or amiodarone) were measured after right ventricular stimulation in all Group I patients. In Group II, serum drug levels were measured after right ventricular stimulation in 21 of 38 drug trials and after left ventricular stimulation in all.

Chronic drug therapy and follow-up: Chronic drug therapy was adjusted to yield serum drug levels that matched drug levels tested in the laboratory. Group I patients were treated chronically with agents that prevented VT induction by right ventricular apical stimulation (Table I).

Based on the results of left ventricular stimulation, Group II patients were divided into 3 groups:

Group IIA consisted of patients in whom no VT was inducible with left ventricular programmed stimulation. These patients were treated chronically with agents found to prevent VT induction in the laboratory (Table I).

Group IIB consisted of patients in whom nonsustained VT was inducible with left ventricular stimulation. One of these patients underwent coronary artery bypass grafting with map-directed endocardial resection and was excluded from chronic follow-up. The remainder of patients in this group were treated chronically with agents that were tested in the laboratory and found to prevent induction of sustained but not unsustained VT (Table I).

Group IIC contained the patients in whom sustained VT was inducible. These patients underwent further drug testing. If sustained VT could no longer be induced, they were then assigned to Group IIA or IIB. In 4 patients, the induction of sustained VT could not be suppressed by any drug regimen tested; these patients were excluded from long-term follow-up in this study. (They were treated with amiodarone and have had no recurrence of symptomatic VT over 12 to 18 months.)

Patients were followed on a regular basis by either 1 of the authors or by the patient's referring physician. Twenty-four hour ambulatory electrocardiographic recordings were obtained every 3 to 4 months. Referring physicians were questioned periodically regarding changes in drug therapy and recurrence of symptoms. Patients were excluded from further follow-up if and when there was a change in drug therapy. Sudden death was defined as unexpected death within 1 hour of the patient's collapse.

Statistical analysis: Values are expressed as mean ± standard deviation. Statistical analysis were performed either with Fisher's exact test or unpaired Student's t test. A paired t test was used to compare serum procainamide or quinidine levels measured immediately after right and left ventricular stimulation in Group II patients.

Results

Patient characteristics: Patients in Group I had 4.0 ± 5.2 episodes of symptomatic VT or VF over 9.9 ± 13.5 months before inclusion in this study. Patients in Group II had 6.6 ± 7.6 episodes of symptomatic VT or VF over 10.9 ± 20.3 months. There was no significant difference between the 2 groups either in the number of episodes of VT or VF or in the duration of symptoms ($p > 0.05$). A similar proportion of patients in Groups I and II, 10 of 30 (33%) and 14 of 34 (41%), respectively, had had at least 1 episode of VF ($p > 0.05$).

There was no significant difference between patients in Groups I and II in regard to age, sex ratio, prevalence of underlying heart disease, left ventricular ejection fraction, percentage of patients with previous myocardial infarction, and percentage of patients with congestive heart failure ($p > 0.05$, Table II).

Results of left ventricular programmed stimulation: In 38 drug trials in which VT could not be induced with programmed stimulation of the right ventricular apex, left ventricular stimulation yielded the following results: (1) no induction of VT in 19 (50%); (2) induction of nonsustained (but not sustained) VT in 10 (26%); and (3) induction of sustained VT in 9 (24%). No complications were encountered as a result of left ventricular programmed stimulation.

Ventricular effective refractory periods: There was no significant difference between the right and left VERP either within or between Groups IIA, IIB, or IIC (Table III).

TABLE I Chronic Drug Therapy in Patients Treated Based on Results of Right Ventricular Stimulation (Group I) and Right and Left Ventricular Stimulation (Group II)

Drug	Group I	Group IIA*	Group IIB†
P, Q, or D	13	11	3
Pr or N	2	1	2
T	1	...	...
A	1	1	1
P and D or Q	3	...	...
P and Pr or N	3	3	2
P and A	...	1	...
Q and Pr	1	...	1
Q and T	...	1	1
Q and Ph	1	...	...
D and Pr	2	...	...
P and D and Pr	1	...	...
P and D and N	...	1	...
Q and D and Pr	1	...	...
Q and T and Pr	1	...	...

* No ventricular tachycardia induced with right or left ventricular stimulation. † Nonsustained ventricular tachycardia induced with left ventricular stimulation.

A = amiodarone; D = disopyramide; N = nadolol, P = procainamide; Ph = phenytoin; Pr = propranolol; Q = quinidine; T = tocainide.

TABLE II Clinical Comparison of Patients Undergoing Right Ventricular Stimulation (Group I) Versus Right and Left Ventricular Stimulation (Group II)

	Group I	Group II*
Patients (n)	30	34
Age (yr)†	58 ± 14.5	53 ± 14.6
Males/females	21/9	24/10
Heart disease‡		
Coronary artery disease	20 (67)	21 (62)
Previous myocardial infarction	19 (63)	19 (56)
Congestive or hypertrophic cardiomyopathy	3 (10)	5 (15)
Mitral valve prolapse	3 (10)	5 (15)
Other	4 (13)	3 (8)
Left ventricular ejection fraction†	0.44 ± 0.18	0.42 ± 0.23
Congestive heart failure†		
I–II§	9 (30)	10 (29)
III–IV§	8 (27)	10 (29)

* There is no statistically significant difference between the 2 groups for any of the variables listed ($p > 0.05$).

† Mean ± standard deviation.

‡ Numbers in parentheses are percentages.

§ New York Heart Association functional class.

TABLE III Ventricular Effective Refractory Periods in Patients Undergoing Right and Left Ventricular Stimulation During Drug Testing*

Group	Results of LV PS	Right VERP (ms)	Left VERP (ms)
IIA	No VT	276 ± 31	277 ± 45
IIB	Nonsustained VT	290 ± 38	275 ± 48
IIC	Sustained VT	293 ± 23	297 ± 32

* Values are expressed as mean ± standard deviation. There were no statistically significant differences between the right and left VERPs either between or within the three groups ($p > 0.05$).

LV PS = left ventricular programmed stimulation; VERP = ventricular effective refractory period; VT = ventricular tachycardia.

TABLE IV Serum Drug Levels Measured Immediately After Right and Left Ventricular Stimulation*

	Group IIA		Group IIB		Group IIC
	Procainamide (9)	Quinidine (3)	Procainamide (3)	Quinidine (2)	Procainamide (4)
RV PS	10.1 ± 5.0	1.7 ± 0.7	14.2 ± 5.1	1.5 ± 0.6	9.2 ± 2.4
LV PS	9.0 ± 4.3	1.5 ± 0.8	13.6 ± 4.5	1.4 ± 0.6	8.6 ± 2.2

* Numbers in parentheses represent the number of drug trials in which drug levels were measured after RV and LV PS. Values are expressed as μg/ml (mean ± standard deviation); there were no statistically significant differences in the serum drug levels measured after right and left ventricular stimulation.

LV = left ventricular; PS = programmed stimulation; RV = right ventricular.

Serum drug levels during programmed ventricular stimulation: There was no significant difference in the serum procainamide or quinidine levels measured immediately after right and left ventricular programmed stimulation in Groups IIA, IIB, or IIC regardless of whether the drugs were tested after oral or intravenous administration (Table IV).

Characteristics of induced ventricular tachycardia: In Group IIB, the mean duration of the induced nonsustained VT was 17 ± 15 beats (range 7 to 48). The mean cycle length of VT was 266 ± 56 ms. The morphology of the induced VT was identical to that of the clinical VT in 5 of 10 cases. In 4 cases the morphology of the clinical VT was unknown, and in 1 case the clinical arrhythmia was VF. VT was induced with 2 left ventricular extrastimuli in 3 patients and with 3 extrastimuli in 7.

In Group IIC, the mean cycle length of the induced sustained VT was 307 ± 72 ms. The morphology of the induced VT was identical to that of the clinical VT in 5 of 9 cases. In 1 case the clinical VT had a right bundle branch block-superior axis configuration, while the induced VT had a right bundle branch block-inferior axis configuration. In 1 case the morphology of the clinical VT was unknown, and in 2 cases the clinical arrhythmia was VF. The method of VT induction consisted of 3 left ventricular extrastimuli in all cases except 1 in which VT was induced with left ventricular overdrive pacing at a cycle length of 300 ms.

Follow-up: In Group I, the overall duration of follow-up was 15.8 ± 11.5 months. Twenty-two of 30 patients (73%) have had no recurrence of symptomatic VT or VF over 20.6 ± 9.4 months. Five patients (17%) had sudden death and 3 (10%) had a nonfatal recurrence of VT at a mean follow-up time of 2.4 ± 2.2 months.

In Group IIA, the mean duration of follow-up has been 13.6 ± 3.7 months. None of the 19 patients has had a recurrence of symptomatic VT or VF. This recurrence rate of zero is significantly lower than the 27% VT/VF recurrence rate in Group I ($p < 0.02$).

In Group IIB, the overall follow-up time was 12.1 ± 4.9 months. Eight of 10 patients (80%) remained free of symptomatic VT or VF. One patient had sudden death at 1 month of follow-up, and 1 had aborted sudden death at 13 months. This 20% recurrence of malignant ventricular arrhythmias was not significantly different from the recurrence rate in either Group I or IIA ($p > 0.05$).

Discussion

This study evaluated the results of left ventricular programmed stimulation in patients who had no inducible VT with right ventricular stimulation during drug testing. Left ventricular stimulation induced nonsustained VT in 26% of drug trials and sustained VT in 24%. Thus, if programmed stimulation of only the right ventricular apex is performed during electrophysiologic drug testing in patients with malignant ventricular arrhythmias, approximately 50% of drug trials may be incorrectly judged as effectively suppressing the induction of VT.

The clinical importance of stimulation at more than 1 ventricular site is demonstrated by comparing the long-term follow-up of patients treated with antiarrhythmic drugs that prevent VT induction with right ventricular versus right and left ventricular stimulation. In this study, 27% of patients who had no inducible VT with right ventricular apical stimulation during drug testing nevertheless had a recurrence of VT or sudden death. In contrast, among patients in whom VT could not be induced with programmed stimulation of either the right or left ventricular apex during drug testing, the recurrence rate of VT and sudden death was zero ($p < 0.02$). The predictive value of left ventricular stimulation in patients who have no inducible VT with programmed stimulation of the right ventricular apex during drug testing is also suggested by the 20% recurrence rate of VT or sudden death in patients who were treated with agents that did not suppress the induction of nonsustained VT with left ventricular stimulation; however, the difference between this recurrence rate and the zero percent recurrence rate in Group IIA patients was not statistically significant.

In previous studies of the predictive value of electrophysiologic drug testing, left ventricular stimulation was performed during drug testing only when stimulation of the left ventricle was required to induce VT before administration of antiarrhythmic drugs.[3,5] Because 89% of patients with clinically documented VT can be induced to have VT with stimulation of the right ven-

tricle,[8] only a small number of patients in previous reports underwent left ventricular stimulation. In the largest published series on the predictive value of electrophysiologic drug testing, only patients who had VT inducible with right ventricular stimulation (pacing site unspecified) were included in the study, and left ventricular stimulation was not performed during drug testing.[6] Over the 18 months of follow-up, malignant ventricular arrhythmias recurred in 32% of 36 patients treated with drugs predicted to be effective. This arrhythmia recurrence rate is similar to the 27% failure rate over 13.9 months in the 30 patients in the present series treated with drugs predicted to be effective on the basis of right ventricular apical stimulation alone. Thus, electrophysiologic drug testing that includes stimulation of only the right ventricular apex may yield suboptimal results.

The induction of VT with left but not right ventricular stimulation in Group IIB and IIC patients was not related to a difference in the right and left VERPs. In addition, serum levels of measurable drugs such as procainamide and quinidine were similar during right and left ventricular stimulation. We postulate that after administration of antiarrhythmic drugs, extrastimuli introduced in the right ventricular apex might no longer reach a potential reentry circuit in the left ventricle due to an intervening area of conduction block; alternatively, after administration of antiarrhythmic drugs, extrastimuli from the right ventricular apex may no longer produce the appropriate temporal relation between unidirectional block and slowed conduction within a potential reentry circuit necessary to initiate VT. However, extrastimuli introduced in the left ventricle, because of closer proximity to the potential reentry circuit, may be able to penetrate the circuit and satisfy the appropriate criteria to induce VT.

Limitations: Our study has several limitations. The assignment of patients to Group I or II was made neither randomly nor concurrently; that is, Group I consists of all patients evaluated before January 1980 plus patients evaluated later in whom left ventricular stimulation was not feasible. However, the clinical characteristics of the patients in Groups I and IIA were similar. In addition, there were no changes in our ventricular stimulation protocol or drug testing protocol since January 1980 other than the addition of left ventricular stimulation. Thus, we do not believe that any significant bias was introduced into the comparison of outcome in Groups I and II.

A second limitation in our study relates to the fact that many Group II patients (57%) were being treated with antiarrhythmic drugs at the time of their initial ventricular stimulation study. Thus, VT was induced with right ventricular apical stimulation in only 46% of Group II patients. However, based on our experience with stimulation of the right ventricle with 3 extrastimuli, we believe that approximately 90% of Group II patients would have had inducible VT if not for treatment with antiarrhythmic drugs during their initial study.

A critical evaluation of the importance of left ventricular programmed stimulation would require a control group of patients treated chronically with agents that prevented VT induction with right but not left ventricular stimulation. However, we did not think it ethical to treat patients chronically with drugs that did not suppress the induction of sustained VT. Thus, the clinical significance of sustained VT induced by left ventricular stimulation during drug testing must be inferred from the higher recurrence rate of VT and sudden death in the Group I patients, who underwent stimulation of only the right ventricular apex. In addition, based on the 20% recurrence rate of VT and sudden death in Group IIB patients, we no longer treat patients chronically with drugs that do not suppress the induction of nonsustained VT with left ventricular programmed stimulation.

An additional limitation in our study is that the maximal duration of follow-up in Group I (35 months) was longer than in Group IIA (22 months). However, because recurrent VT and sudden death in Group I patients occurred at a mean follow-up time of 2.4 ± 2.2 months, we think it is unlikely that the significantly lower recurrence rate of malignant ventricular arrhythmias in Group IIA patients is attributable to the shorter maximum duration of follow-up.

A final potential limitation of our study is that right ventricular stimulation was performed in only 1 location, the apex. We cannot rule out the possibility that stimulation at other right ventricular sites such as the septum or outflow tract would have induced VT during drug testing in our Group II patients and thus precluded the need for left ventricular stimulation. The results of our study should not be construed as necessarily suggesting the need for left ventricular stimulation during drug testing in patients in whom VT cannot be induced from the right ventricle. The importance of our observations is related to the finding that inability to induce ventricular tachycardia from 1 ventricular site after drug testing does not preclude inducibility from other ventricular sites. This finding appears to have important clinical implications.

Conclusions: Despite the foregoing limitations in our study, the following conclusions can be drawn with regard to electrophysiologic drug testing in patients with malignant ventricular arrhythmias: (1) As previously reported,[12] programmed stimulation of the left ventricle can be performed safely. (2) In patients in whom VT cannot be induced with stimulation of the right ventricular apex, left ventricular stimulation results in the induction of sustained VT in approximately 25% and nonsustained also in approximately 25%. (3) Induction of VT with left ventricular stimulation is not related to a difference between right and left ventricular effective refractory periods. (4) Drug therapy that suppresses VT induction with both right and left ventricular stimulation results in a significantly better clinical response than therapy based on stimulation of only the right ventricular apex; thus, during drug testing, stimulation should not be limited to the right ventricular apex, even when VT is inducible from this site in the baseline state. Whether or not stimulation from multiple right ventricular sites will preclude the need for left ventricular stimulation remains to be determined.

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Electrophysiologic Study for Ventricular Arrhythmia: Effect on Total and Myocardial-Specific Creatine Kinase Activity

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To determine the potential for myocardial injury during electrophysiologic study for ventricular arrhythmia, total creatine kinase and creatine kinase B-subunit enzyme activity were serially measured after the procedure in 24 patients. During electrophysiologic study 14 of the 24 patients had sustained ventricular tachycardia or fibrillation, 4 patients had nonsustained ventricular tachycardia, and 6 patients had no ventricular arrhythmia induced. Cardioversion was necessary because of hemodynamic collapse in 9 of the 14 patients with sustained ventricular tachycardia or ventricular fibrillation. Coronary heart disease was present in 14 of the 24 patients, in 9 of the 14 with sustained ventricular tachycardia or ventricular fibrillation, and in 7 of the 9 patients requiring cardioversion. Total creatine kinase was modestly elevated (greater than twice baseline or greater than normal, or both) 24 hours after electrophysiologic study in 10 (42%) of the patients. Electrophysiologic study with or without the induction of ventricular tachycardia or ventricular fibrillation was not associated with increased creatine kinase B-subunit activity even in patients with coronary heart disease.

Currently, the management of life-threatening ventricular arrhythmias, particularly those associated with severe ischemic heart disease, may include the use of programmed stimulation of the heart.[1–4] Frequently, sustained ventricular tachycardia or fibrillation induced by programmed stimulation, such as spontaneous arrhythmia, requires emergency cardioversion. To date, the presence and extent of myocardial damage resulting from insertion of the electrode catheter, programmed stimulation, and induction of ventricular arrhythmia have not been evaluated.

In the present study, total creatine kinase and creatine kinase B-subunit activity, using the Merck immunoinhibition technique, were serially measured after electrophysiologic testing in 24 patients undergoing evaluation of ventricular arrhythmia. The study was designed (1) to assess the effects of electrophysiologic study on total creatine kinase activity, and (2) to determine whether myocardial injury, as reflected by creatine kinase B-subunit activity, occurs during programmed stimulation and induction of arrhythmia, particularly in patients with severe coronary heart disease and ventricular arrhythmias resulting in hemodynamic collapse.

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Methods

Patients (Table I): The patients included 18 men and 6 women, aged 16 to 84 years (mean 54.4), undergoing electrophysiologic study for evaluation and therapy of documented or suspected ventricular tachyarrhythmia. Fourteen patients had documented sustained ventricular tachycardia or fibrillation which produced life-threatening symptoms or failed to respond to standard antiarrhythmic drug therapy, or both. The remaining 10 patients had electrocardiographic demonstration of complex ventricular ectopic activity and symptoms of dizziness or syncope.

Fourteen of the 24 patients had coronary heart disease, 3 had idiopathic congestive cardiomyopathy, 1 had rheumatic valve disease, and 6 had no evidence of organic heart disease

TABLE I Arrhythmia Induced and Creatine Kinase (CK) Activity After Electrophysiologic Study

Case	Age (yr) & Sex	Cardiac Diagnosis	Arrhythmia Induced	DC Shock Delivered Energy*	Elevated Total CK (Peak)†	Elevated B-Subunit CK‡
1	59F	Normal	None	. . .	No	No
2	56F	ASHD LVAn	VT	100(1)	No	No
3	34F	CCM	VT	50(1)	Yes (58.6)	No
4	44M	ASHD LVAn	VT	740(4)	Yes (123.3)	No
5	61M	ASHD	None	. . .	Yes (115.2)	No
6	32M	Normal	VT	. . .	No	No
7	50M	ASHD	NSVT	. . .	Yes (185.8)	No
8	49M	ASHD	VT	520(3)	Yes (122.1)	No
9	61M	ASHD	NSVT	. . .	No	No
10	16M	Normal	VT	. . .	No	No
11	55M	Normal	None	. . .	No	No
12	69M	RHD	None	. . .	No	No
13	57F	Normal	None	. . .	Yes (155.2)	No
14	46M	ASHD LVAn	VF	320(1)	No	No
15	60M	CCM	VT	640(2)	Yes (227.3)	No
16	55M	Normal	AF	. . .	Yes (265.3)	No
17	84F	ASHD	NSVT	. . .	No	No
18	57M	ASHD LVAn	VT	420(2)	No	No
19	63M	ASHD LVAn	VT	450(3)	Yes (116.4)	No
20	68F	CCM	VT	. . .	No	No
21	43M	ASHD	VT	100(1)	No	No
22	45M	ASHD	NSVT	. . .	Yes (196.8)	No
23	71M	ASHD LVAn	VT	. . .	No	No
24	61M	ASHD LVAn	VT	. . .	No	No

* Total delivered energy in joules. The number of shocks is indicated in parentheses. † Elevated total CK activity equals greater than the upper reference limits (see text) or greater than twice the baseline value, or both. Peak value is indicated in parentheses in units/liter. ‡ Elevated CK B-subunit activity equals greater than the upper reference limit of 13 U/liter.

AF = atrial fibrillation; ASHD = atherosclerotic heart disease; CCM = congestive; DC = direct current; cardiomyopathy; LVAn = left ventricular aneurysm; NSVT = nonsustained ventricular tachycardia; RHD = rheumatic heart disease; VF = ventricular fibrillation; VT = ventricular tachycardia.

by cardiac catheterization (4 patients) or gated blood pool scan and echocardiogram (2 patients). Cardiac catheterization was performed in 11 of 14 patients with coronary heart disease. Three patients had single vessel disease, and 4 patients had double and triple vessel disease as judged by 70% or greater obstruction.

None of the 24 patients had intramuscular injections, anginal chest pain, cardiac catheterization, or muscle trauma in the 72 hours before or 24 hours after electrophysiologic study.

Electrophysiologic testing: Studies were performed while the patients were in a nonsedated, postabsorptive state. All venous catheters, except 1, were inserted percutaneously at femoral (54 catheters) or antecubital (15 catheters) sites. One venous catheter was inserted through an antecubital cutdown. Left ventricular catheterization, for the purpose of programmed stimulation or activation mapping of sustained tachycardia, was performed in 9 patients using a femoral arterial percutaneous approach.

The stimulation protocol included the introduction of 1 to 3 ventricular extrastimuli after 8 spontaneous or paced beats at multiple cycle lengths. If ventricular tachycardia or fibrillation was not induced by extrastimuli from up to 3 right ventricular sites, rapid ventricular pacing from the right ventricle at cycle lengths of 350 to 250 ms for 15 seconds was performed. In 7 of the 24 patients up to 3 ventricular extrastimuli were introduced from multiple left ventricular sites after right ventricular stimulation failed to induce tachyarrhythmia. In 19 patients programmed atrial stimulation was also performed. Stimulation was performed with a custom-designed programmable stimulator (Bloom Associates, Narberth, Pennsylvania) using 1 ms impulses at twice diastolic threshold. After completion of the electrophysiologic study, catheters were removed in all patients except 1 (Case 6) in whom a size 6 Fr electrode catheter was left in place at the right ventricular apex for serial drug studies.

Electrical countershock was performed when necessary during electrophysiologic testing using a Bectin-Dickenson Electrodyne cardioverter. The electrode paddle size was 8 cm. After liberal application of redux paste, anterior paddles were positioned for cardioversion just to the right of the sternum at the level of the first and second ribs and in the left anterior axillary line. Maximal deliverable energy capacity for the cardioverter is 320 W-s.

Biochemical procedures: Blood samples were obtained at the time of and 4, 8, and 24 hours after the electrophysiologic study from each of the 24 patients. Baseline samples were obtained immediately before catheter insertion in 18 patients and after catheter insertion in 6 patients. To avoid the possibility of missing small peaks in the total creatine kinase or creatine kinase B-subunit activity during the first 12 hours and to help find the pattern of creatine kinase elevation, we took samples at 2 hour intervals after the study for the first 12 hours, and then at 24 hours in the first 8 patients. Because no elevation in creatine kinase B-subunit activity was observed in these patients, and elevated total creatine kinase activity appeared to consistently peak after the first 12 hours, in the remaining patients samples were obtained less often:

4, 8, and 24 hours after electrophysiologic study (see Results). In addition, reference limits were determined by measuring total creatine kinase (160 subjects) and creatine kinase B-subunit (201 subjects) enzyme activity in asymptomatic ambulatory volunteers.

Each blood sample was allowed to clot at room temperature, centrifuged at 2,000 *g* for 10 minutes and decanted. Creatine kinase determinations were performed within 24 hours on the refrigerated (4°C) samples, or else the sample was stored for a maximum of 120 hours in a freezer at −20°C until analysis could be performed. Total creatine kinase activity was assayed kinetically at 37°C by the method of Szasz et al.[5]

Creatine kinase B-subunit dependent activity was determined at 37°C as the creatine kinase activity remaining after immunoinhibition with a creatine kinase M-subunit inhibiting antibody (anti-M). Because residual adenylate kinase activity from erythrocytes and other tissues can falsely elevate creatine kinase B-subunit activity, residual adenylate kinase activity was measured in all samples and subtracted from the apparent creatine kinase B-subunit activity if B-subunit activity exceeded the upper reference limit.[6]

The value of total creatine kinase and creatine kinase B-subunit activity was considered elevated if the value exceeded the normal range. In addition, total creatine kinase activity was also designated as elevated if the value increased by more than 2 times the baseline value. A twofold or more increase is significantly greater than the normal day-to-day variation in total creatine kinase activity of 25%.[7] Statistical methods included chi-square analysis and Student's *t* test for unpaired data when appropriate.

Results

Electrophysiologic studies: The duration of the electrophysiologic studies averaged 3 hours (range 1 to 4.5). An average of 3.1 (range 1 to 5) electrode catheters were used for each patient. No complications were noted during the study. No patient undergoing intracardiac electrophysiologic evaluation had clinical or electrocardiographic evidence of myocardial infarction.

Arrhythmias induced (Table I): Sustained ventricular tachycardia was initiated in 13 patients and ventricular fibrillation in 1. Four patients had only nonsustained ventricular tachycardia (7 to 26 beats) reproducibly initiated. One patient had atrial fibrillation induced by programmed stimulation. In the remaining 5 patients, no arrhythmias were initiated.

Methods of arrhythmia termination: Nine of the 14 patients with sustained ventricular arrhythmias during electrophysiologic testing required cardioversion because of rapid (less than 60 seconds lapsed time) hemodynamic collapse associated with loss of consciousness (Table I). Cardioversion was performed immediately upon the patient's loss of consciousness. Repetitive shocks were required in 5 patients. Total cumulative delivered energy required for cardioversion was 50 to 740 W-s.

In the 5 remaining patients with induced sustained ventricular tachycardia, the tachycardia was terminated by rapid ventricular pacing. Pacing terminated tachycardia within 5 minutes of onset in 4 patients and after 1 hour in the fifth patient, during which time left ventricular activation mapping was performed. Cuff blood pressure recordings obtained in 3 of the 5 patients demonstrated a systolic blood pressure recording of 100 mm Hg or greater and were within 20 mm Hg of baseline systolic blood pressure. In the remaining 2 patients ventricular tachycardia was terminated before cuff blood pressure could be obtained. One patient complained of anginal chest pain during the tachycardia.

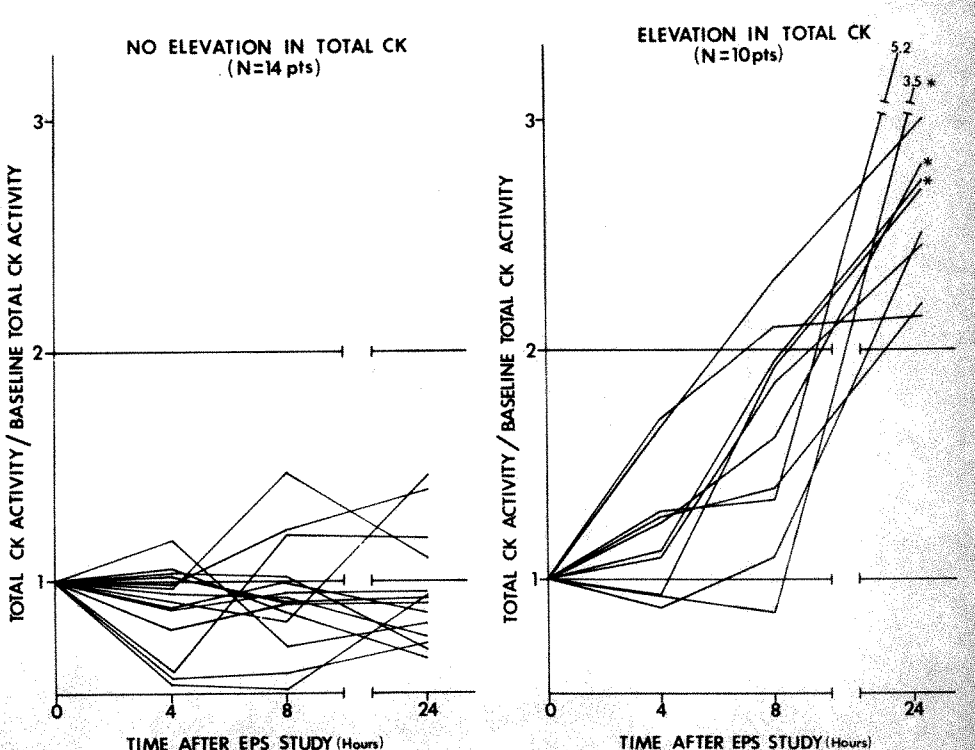

FIGURE 1. Pattern of total creatine kinase activity after electrophysiologic testing (EPS) for ventricular arrhythmias in the 14 patients without **(left panel)** and the 10 patients with **(right panel)** an elevation in total enzyme activity. Total creatine kinase (CK) activity after the study is compared with a baseline value (time = 0) of unity. Elevated total creatine kinase activity (greater than twice the baseline value) is noted at 24 hours in all 10 patients. **Asterisk,** peak total creatine kinase activity greater than upper reference limit.

The pain resolved within 30 seconds after termination of the arrhythmia by rapid pacing.

Effect on total and B-subunit creatine kinase activity: Reference limits for total creatine kinase activity were 22 to 222 units/liter in men and 34 and 140 units/liter in women. Changes in total creatine kinase activity after electrophysiologic study compared with a baseline value of unity are shown graphically in Figure 1. In 10 of 24 patients (42%), total creatine kinase activity after electrophysiologic study increased by more than twice the baseline value (Table I). All elevations in total creatine kinase activity were evident at 24 hours. However, in 2 patients, Cases 4 and 19, elevation was apparent as early as 8 hours.

The presence of coronary heart disease, arrhythmia induction, left ventricular catheterization, and the need for cardioversion did not significantly ($p > 0.05$) influence the likelihood of elevated total creatine kinase activity after electrophysiologic study. However, all 4 patients in whom delivered energy during cardioversion was 450 W-s or more had an elevation in total creatine kinase activity (Table I). Patients with elevations in total creatine kinase activity did not differ significantly from the group in which elevation was not observed with respect to the duration of electrophysiologic study (3.2 ± 0.7 versus 3.0 ± 1.0 hours) or the number of catheters used during the procedure (3.4 ± 0.7 versus 2.9 ± 1.2).

Creatine kinase B-subunit activity determined in the 201 control subjects established reference limits of 3 to 13 units/liter. B-subunit activity was below the upper reference limit at each time interval after electrophysiologic study in all 24 patients (Fig. 2). Furthermore, B-subunit activity did not increase by twice the baseline value in any patient. Thus, the elevation in total creatine kinase activity observed was due to creatine kinase MM isoenzyme rather than myocardial specific B-subunit activity.

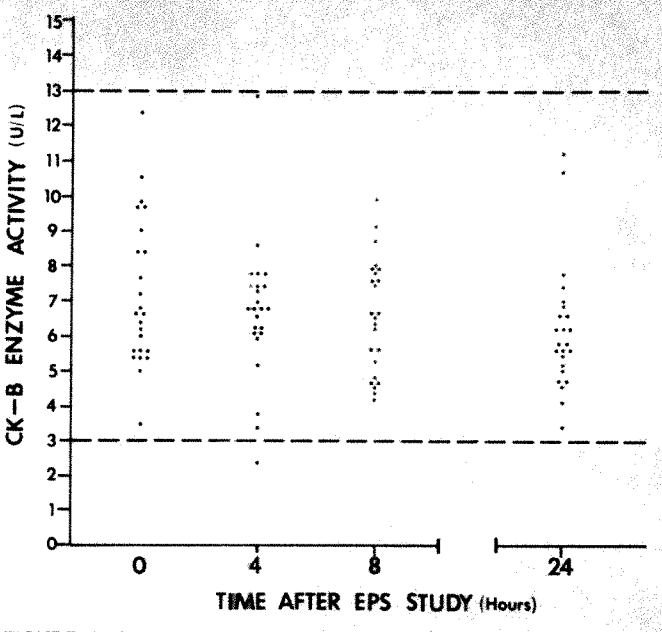

FIGURE 2. Creatine kinase B-subunit (CK-B) activity after electrophysiologic study for ventricular arrhythmia. **Dashed lines** mark the reference limits for B-subunit enzyme activity. All values for creatine kinase B-subunit activity fell below the upper reference limit at each time interval after the study. U/L = units/liter.

Discussion

Electrophysiologic studies are becoming more widely used for the diagnosis and therapy of malignant ventricular arrhythmias. The most common anatomic substrate associated with sustained ventricular tachycardia or fibrillation is severe multivessel coronary heart disease, usually with prior myocardial infarction, and often complicated by ventricular aneurysm formation.[8–10] Concern exists that induction of arrhythmia, particularly in patients with extensive coronary heart disease, might result in myocardial injury.[11] Accordingly, we sought to determine whether myocardial injury results from electrophysiologic studies for ventricular arrhythmias that involve (1) cardiac catheterization with electrode catheters, (2) programmed stimulation to attempt arrhythmia induction, and (3) the development of arrhythmias that frequently, similar to spontaneous arrhythmias, lead to hemodynamic collapse and require electrical countershock to restore normal sinus rhythm.

Elevation in total but not myocardial specific creatine kinase activity has been observed in 38 to 80% of patients after uncomplicated hemodynamic and angiographic cardiac catheterization.[12–15] Activity was reported to increase progressively and peak 12 to 24 hours after cardiac catheterization.[12–15] The increased total creatine kinase activity after cardiac catheterization is presumed to be related to either trauma to soft tissue or intramuscular injection of premedication. In addition, a modest increase in total creatine kinase activity has been reported in 6 to 50% of patients after elective electrical countershock of predominantly supraventricular arrhythmias.[16–18] More rarely, a slight elevation in MB creatine kinase coincident with total creatine kinase peak activity has been documented.[17] Other reports in animal models have suggested that there is potential for myocardial injury during closed-chest electrical countershock.[19]

In the present study total creatine kinase activity was elevated (greater than twice control values or greater than normal values, or both) in 42% of patients after electrophysiologic study. Arrhythmia induction or cardiac diagnosis did not influence total creatine kinase activity. All 4 patients who received at least 450 W-s of energy delivered during electrical cardioversion had an increase in total creatine kinase activity. Chest wall trauma related to the electrical countershock may have contributed to this increase. However, peak creatine kinase activity after electrical countershock has been observed to occur within 4 to 6 hours of the event.[17] Our findings of a more marked delay before maximal creatine kinase activity over a 24 hour period suggests that in our patients chest wall muscle trauma was not the only contributor to the increased total creatine kinase activity observed. The observation that total creatine

kinase activity became elevated 8 to 24 hours after electrophysiologic study is similar to the timing of the elevation after hemodynamic and angiographic cardiac catheterization.[12,13] Trauma to soft tissue related to catheter insertion may be the common denominator because none of our patients received intramuscular injections.

We found that creatine kinase B-subunit activity, which was determined after immunoinhibition of M-subunit activity, did not increase in any patient after electrophysiologic study. Because BB activity contributes negligibly to total B-subunit activity, creatine kinase B-subunit activity has been demonstrated almost uniformly to reflect myocardial specific MB activity.[20–22] Ljungdahl et al.[23] have demonstrated the effectiveness and sensitivity of measuring B-subunit activity in determining myocardial injury in patients with acute chest pain syndromes. Furthermore, Elser et al.[24] reported comparable sensitivity and specificity of B-subunit activity, measured 8 to 32 hours after suspected acute myocardial infarction, with MB activity measured using electrophoretic or chromatographic techniques. Thus, despite the fact that most of our patients had severe coronary heart disease, we could demonstrate no evidence of myocardial injury related to the stimulation procedure or arrhythmia induction as reflected by an increase in creatine kinase B-subunit activity.

It appears that electrophysiologic study including the induction of sustained ventricular tachyarrhythmia can safely be performed even in patients with underlying coronary heart disease. Nevertheless, the potential for myocardial damage during electrophysiologic study should not be ignored. Experienced and skilled technical assistance is crucial for reestablishing and maintaining electrocardiographic and hemodynamic stability.

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Amiodarone for Control of Sustained Ventricular Tachyarrhythmia: Clinical and Electrophysiologic Effects in 51 Patients

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We evaluated the electrophysiologic effects of amiodarone and its ability to control ventricular arrhythmia in a selected group of 51 patients with refractory sustained ventricular arrhythmia. Amiodarone in doses of 400 to 800 mg/day prolonged refractoriness in the atria, atrioventricular (AV) node, and ventricle as well as conduction through the AV node and His-Purkinje system. Although it had no effect on measurements of sinus nodal function (sinus nodal recovery time and sinoatrial conduction time), it prolonged the sinus cycle length and 2 patients required a permanent pacemaker for symptomatic sinus bradycardia. Amiodarone did not alter the ease of inducibility in any consistent manner, and only 5 of 43 patients (12%) who had inducible ventricular tachycardia before amiodarone therapy had none induced during amiodarone treatment. The clinical effectiveness of amiodarone could be evaluated in 46 patients followed up for 8.6 ± 6 months (range 0.5 to 22). It provided effective therapy in 23 patients (50%), partly effective therapy in 13 (28%), and was ineffective in 10 (22%). Adverse effects were noted in 28 of 51 patients (55%), and in 11 of these (22%) the drug had to be discontinued because of adverse effects.

We conclude that amiodarone is a useful agent for the treatment of refractory sustained ventricular arrhythmia. Its use should be reserved for patients with life-threatening sustained arrhythmia because of the significant incidence of adverse effects. Furthermore, good clinical response can be observed in patients receiving amiodarone in spite of continued inducibility.

Amiodarone hydrochloride is a benzofuran derivative which was first introduced as a coronary vasodilator and antianginal agent almost 20 years ago.[1,2] It was later discovered that amiodarone has antiarrhythmic properties and that its major effect is on action potential duration (class III antiarrhythmic agent).[3–5] Amiodarone is an attractive antiarrhythmic agent because it may be administered only once a day and is relatively nontoxic.[6–9] Studies in Europe, South America, and Canada[6–8,10,11] have suggested that amiodarone is effective for the treatment of both supraventricular and ventricular arrhythmia. The present study was undertaken to evaluate the electrophysiologic and clinical effects of oral amiodarone in a selected group of 51 patients with medically refractory sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), or both.

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Methods

Patients: The study group consisted of 51 patients (41 men and 10 women, aged 17 to 74 years) with medically refractory (see later) VT or VF. All patients except 1 (Case 11) had evidence of organic heart disease: coronary artery disease in 39, idiopathic cardiomyopathy in 5, mitral valve prolapse in 2, hypertensive cardiovascular disease in 1, hypertrophic cardiomyopathy in 1, left ventricular aneurysm in the absence of coronary artery disease in 1, and arrhythmogenic right ventricular dysplasia in 1.

All patients with a diagnosis of coronary heart disease had had at least 1 myocardial infarction. Infarction occurred at least 1 month before starting amiodarone therapy. Thirteen of the 39 patients with coronary heart disease had a left ventricular aneurysm when amiodarone was first administered. Nine of 39 patients had undergone prior left ventricular aneurysmectomy either for attempted control of VT (7 patients) or for hemodynamic indications (2 patients).

Left ventricular ejection fraction by nuclear blood pool scan or cardiac catheterization was measured in 44 of the 51 patients and was found to be 37 ± 17% (range 10 to 77); in 31 of the 39 patients with coronary artery disease, it was 30 ± 13% (range 10 to 67).

All patients had 1 to more than 100 episodes of sustained VT, cardiac arrest, or both, before amiodarone treatment was begun. Nineteen of the 51 patients (37%) had at least 1 cardiac arrest and 4 other patients experienced at least 1 syncopal episode. Thirty-nine patients (76%) required 1 to over 25 cardioversions for the termination of paroxysmal sustained VT or VF.

Previous antiarrhythmic therapy included 4.5 ± 1 (range 2 to 6) conventional agents per patient, 1 to 5 drug combinations per patient in 33 cases, and at least 1 other experimental antiarrhythmic agent in 14 cases. In some instances medications were discontinued because of the development of intolerable side effects. Failure of conventional or experimental antiarrhythmic agents was based on documented clinical recurrence of a sustained arrhythmia or continued inducibility during intracardiac electrophysiologic testing.

Monitoring facilities: During the initiation of therapy (2 to 3 weeks), all patients were continuously monitored in the Medical Intensive Care Unit or in an adjacent telemetry unit, both utilizing a computerized continuous recall arrhythmia monitoring facility (Becton-Dickinson, Electrodyne). Daily records were reviewed to help determine the effectiveness of treatment.

Electrophysiologic studies were conducted in all 51 patients. In 33 patients the studies could be conducted both before (control study) and after administration of amiodarone alone (treatment study). In 6 patients no antiarrhythmic drugs were given before the control study, but at the treatment study antiarrhythmic drugs in addition to amiodarone were administered because amiodarone alone had not controlled ventricular arrhythmia successfully. In 12 patients a control study during which the patients were taking no antiarrhythmic drugs could not be performed because of the presence of frequent episodic or incessant VT.

Electrophysiologic testing was performed in the nonsedated postabsorptive state after written informed consent was obtained.[12] Three or 4 electrode catheters were inserted percutaneously into the femoral or antecubital veins and positioned under fluoroscopic guidance into the high right atrium, the atrioventricular junction to obtain a recording of the His bundle, the coronary sinus, and the right ventricular apex. Programmed stimulation was performed using pulses of 1 ms duration at twice diastolic threshold using a custom-designed programmable stimulator and an optically isolated constant current source (Bloom Associates, Narberth, Pennsylvania).

The following electrophysiologic measurements were made: Corrected sinus nodal recovery time, sinoatrial conduction time, A-H and H-V intervals during normal sinus rhythm, A-H interval at multiple atrial paced cycle lengths, atrial paced cycle length to AV node Wenckebach conduction, atrial effective refractory period, and ventricular effective refractory period.[13] At least 3 atrial cycle lengths were used to evaluate the corrected sinus nodal recovery time, most often 600, 500, and 400 ms. The length of pacing at each cycle length and the interval between each pacing period was at least 1 minute. The sinus nodal recovery time was corrected by subtracting the sinus cycle length. The sinoatrial conduction time was measured by the Narula method and was divided by 2.[14] Refractory periods were measured at the same paced cycle length and site of stimulation before and after therapy for purposes of comparison.

The stimulation protocol for VT during control and all subsequent studies consisted of the introduction of single, double, and triple ventricular extrastimuli during sinus rhythm or ventricular paced rhythm at multiple cycle lengths (800 to 400 ms), or both, and during bursts of rapid pacing (400 to 250 ms for 15 to 30 seconds) at the right ventricular apex. If VT was not induced using this protocol, similar stimulation was performed at the right ventricular outflow tract. No patient in this series required left ventricular stimulation or isoproterenol for induction. Two catheters were routinely employed during follow-up testing.

Amiodarone administration: Amiodarone therapy was begun with a loading dose of 1,400 mg/day as a single dose with meals for an initial loading period of 11.1 ± 6.6 days (range 7 to 35). During the early portion of the loading period, conventional antiarrhythmic agents were often given, especially in cases of incessant or frequent or very rapid VT.

In the first 25 patients studied, the duration of loading and subsequent maintenance dose of amiodarone was based upon the level of spontaneous ventricular ectopic activity. The patients were continued on a loading dose of amiodarone until continuous monitoring revealed fewer than 6 premature ventricular depolarizations per hour and no triplets or VT for 72 hours. The maintenance dose of amiodarone was derived from the number of days of loading required in Patients 1 through 25 as follows: 7 days or fewer, 400 mg/day; 7 to 14 days, 600 mg/day; and more than 14 days, 800 mg/day. In Patients 26 through 51 the criteria were modified so that the maintenance dose was begun when no VT was detected for 72 hours. Again, the amount of the maintenance dose was based on the number of days of loading.

Electrophysiologic testing on amiodarone was performed after the patients had been on their maintenance dose for 2 to 108 days. Forty-nine of 64 electrophysiologic studies were performed after the patients had been on the maintenance dose for 4 to 8 days. Initially, the patients in whom VT could still be induced were reloaded with 1,400 mg/day and then given a dose 200 mg greater than that they had received previously. Seventeen patients underwent 18 reloading periods (1,400 mg/day) of 4.1 ± 1.4 days (range 2 to 8) followed by 10 ± 11 days of maintenance therapy before repeated electrophysiologic study because of continued inducibility. However, tachycardia was inducible in all patients on amiodarone despite reloading (see Results), and this method was abandoned. Patients were then continued on amiodarone without reloading despite inducibility. Reloading (3 to 8 days of 1,400 mg/day) was performed in 4 other patients because of spontaneous VT occurring after 1 to 20 days on a maintenance dose.

In 9 cases a type I antiarrhythmic agent was added and electrophysiologic testing repeated if amiodarone alone had failed to prevent spontaneous or induced VT. Fifteen patients were treated with a type I antiarrhythmic agent (quinidine, 13; procainamide, 2) in addition to amiodarone either because it slowed the rate of induced VT and we concluded the patients would be more likely to survive a recurrence (5 cases) or for clinical control (10 cases).

Routine laboratory tests before amiodarone and during follow-up included chest x-ray, complete blood count and differential, liver function tests, electrolyte determination, urinalysis, thyroid function tests, electrocardiogram, and ophthalmologic examination. Holter monitoring and nuclear gated blood pool scans were performed before the start of amiodarone therapy when possible. Follow-up evaluation was performed every 1 to 3 months at the University of Pennsylvania, or when the patients lived at a long distance, by the patient's private physician with telephone or mail follow-up

to one of the investigators. Routine laboratory tests, electrocardiogram, 24 hour Holter monitoring, and physical examinations were performed during follow-up visits. Ophthalmologic examinations were performed at similar intervals whenever possible.

All patients received artificial tear solution 4 times a day because it has been suggested that this might lessen the development of corneal microdeposits.[15]

The efficacy of amiodarone was assessed during follow-up with the following criteria: It was judged (a) *effective* if no sustained or symptomatic arrhythmia occurred after a maintenance dose was established, (b) *partly effective* if the frequency of episodes decreased or if another medication that was ineffective alone was effective in combination with amiodarone, and (c) *ineffective* if arrhythmia occurrence was not favorably altered or sudden death occurred.

Statistical analysis of electrophysiologic data was performed using a paired Student's *t* test. Data are expressed as mean ± standard deviation unless otherwise specified.

Results

Electrophysiologic Data (Table I)

Comparison of electrophysiologic effects of amiodarone was made between control values and the highest maintenance dose tested in each patient. Twenty-five patients were taking digoxin, 3 propranolol, and 8 digoxin and propranolol during the control electrophysiologic study. In patients taking digoxin or propranolol, or both, electrophysiologic data were compared only when the dose of these medications were unchanged between the control and the treatment study.

Amiodarone had no statistically significant effect on measurements of sinus nodal function (corrected sinus nodal recovery time and sinoatrial conduction time). However, the sinus cycle length increased by 84 + 202 ms in the 24 patients in whom it could be assessed in the absence of additional agents. Two patients required a permanent pacemaker because of severe symptomatic sinus bradycardia. Amiodarone prolonged the atrial effective refractory period by 42 ± 43 ms in 21 patients ($p < 0.001$), prolonged the A-H interval during sinus rhythm by 14 ± 21 ms in 28 patients ($p < 0.001$), prolonged the A-H interval measured at the same paced cycle length by 40 ± 57 ms in 16 patients ($p < 0.01$), prolonged the paced cycle length to AV node Wenckebach conduction by 113 ± 100 ms in 27 patients ($p < 0.001$), prolonged the H-V interval by 4 ± 9 ms in 35 patients ($p < 0.01$), and prolonged the ventricular effective refractory period by 24 ± 33 ms in 27 patients ($p < 0.001$).

The effects of amiodarone on the H-V interval, although statistically significant, were small. The H-V interval during sinus rhythm was prolonged after amiodarone by 10 to 20 ms in 11 patients. The H-V interval changed by 5 ms or less in 19 patients. In 1 patient infra-His bundle block was observed during atrial pacing at a paced cycle length of 600 ms for which a permanent pacemaker was implanted. This patient had a prolonged H-V interval of 60 ms before starting amiodarone.

Effect of amiodarone on induction and cycle length of VT: VT was induced in the control study in 43 of the 51 patients, 33 of whom were taking no antiarrhythmic drugs. Eight of 51 patients spontaneously developed VT either very frequently or incessantly, and consequently induction was not evaluated. At the treatment study in 5 of 43 patients, VT could no longer be induced. The administration of another antiarrhythmic drug in addition to amiodarone had no effect on inducibility in 9 patients tested. Ease of inducibility was not altered by amiodarone in any consistent fashion (Fig. 1).

The cycle length of 34 episodes of sustained VT induced in 34 patients during the control study (on no antiarrhythmic medication other than digoxin, propranolol, or both) was 303 ± 67 ms, and during the treatment study (on amiodarone alone) was 343 ± 77 ms ($p = 0.01$). Morphologically identical VT was induced during the control study and during the treatment study in 20 patients. The VT cycle length increased from 293 ± 64 to 357 ± 84 ms in these patients ($p < 0.001$) (Fig. 2). In 14 patients the morphology of the VT induced during the control and treatment studies was not identical. However, the morphology of VT induced was similar to that observed either spontaneously or during induction study on other antiarrhythmic drugs in al-

TABLE I Electrophysiologic Data

	Baseline (ms)	Amiodarone (ms)	Difference (ms)	p Value	Patients (n)	Treatment Period (Days)
Sinus cycle length	844 ± 157	928 ± 238	84 ± 202	<0.05	24	30 ± 28
Corrected sinus nodal recovery time	271 ± 118	279 ± 124	8.0 ± 148	NS	25	23 ± 16
Sinoatrial conduction time	90 ± 51	96 ± 47	7.0 ± 45	NS	16	20 ± 14
Atrial effective refractory period	252 ± 40	294 ± 39	42 ± 43	<0.001	21	24 ± 22
A-H (resting)	90 ± 24	105 ± 22	14 ± 21	<0.001	28	25 ± 25
A-H interval (at same paced cycle length)	115 ± 33	155 ± 54	40 ± 57	<0.01	16	18 ± 11
Paced cycle length to AV node Wenckebach	360 ± 61	472 ± 99	113 ± 100	<0.001	27	22 ± 15
H-V interval	62 ± 12	66 ± 13	4 ± 9	<0.01	35	28 ± 25
Ventricular effective refractory period	260 ± 23	284 ± 34	24 ± 33	<0.001	27	31 ± 27

most all cases. The addition of type I antiarrhythmic agent in 9 cases (quinidine in 4, procainamide in 4, and disopramide in 1) resulted in a further significant increase in tachycardia cycle length from 288 ± 67 to 354 ± 95 ms ($p < 0.001$).

Clinical Efficacy of Amiodarone for Control of Ventricular Tachyarrhythmia (Table II)

The clinical value of amiodarone could be evaluated in 46 of the 51 patients. Five patients were not included in long-term evaluation for the following reasons: 2 had left ventricular aneurysmectomy and endocardial resection, 1 was discharged on another agent because of continued inducibility (at a time early in the study when we thought that noninducibility was required for successful treatment), and 2 patients died from congestive heart failure without VT recurrence after 2 and 3 weeks of amiodarone treatment. These 46 patients were followed up for a mean of 8.6 ± 6 months (range 0.5 to 22). All patients except 1 (Case 21, see later) in whom amiodarone was considered effective or partly effective were treated for at least 3 months.

Effective group: Amiodarone provided effective therapy in 23 of 46 patients (50%). In 7 of these patients, amiodarone had to be discontinued because of side effects which developed after 6 to 19 months of treatment. Four other patients died during follow-up. Two patients died from congestive heart failure after 6 and 7 months of therapy, respectively, and 1 died from gram-negative sepsis after 3 months of therapy. One patient died from rapid VT 11 days after amiodarone was discontinued for no apparent reason by the patient's private physician.

Partly effective group: Amiodarone was considered partly effective in 13 of 46 patients (28%). In 3 of these 13 patients, a type I agent was added because of the induction of VT associated with cardiac arrest during electrophysiologic study. The type I agent was administered because it decreased the rate of induced VT to a more tolerable rate, and we concluded that the patients would be more likely to survive a recurrence. A type I antiarrhythmic agent, which was ineffective before amiodarone, was needed in 9 patients for control of spontaneous sustained VT. In 1 patient (Case 26) occasional episodes of VT on amiodarone alone were well tolerated. In this patient the intermittent episodes of VT were terminated at home with an oral dose of procainamide.

Three patients in whom amiodarone was considered partly effective had to have the medication discontinued because of adverse effects which developed after 8, 9, and 18 months of treatment. One patient died from congestive heart failure and 1 from pneumonitis after 1.5 and 5 months of therapy, respectively. In the patient who died from congestive heart failure (Case 21) the combination of amiodarone and quinidine successfully suppressed incessant VT. This was the only patient treated with amiodarone for less than 3 months in whom it was considered either effective or partly effective.

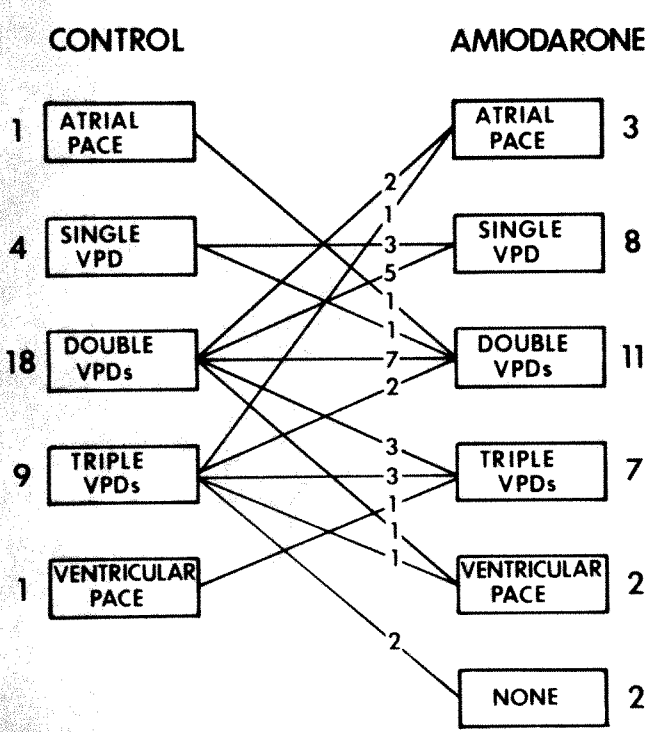


FIGURE 1. Mode of induction of ventricular tachycardia in 33 patients during the control study and during the treatment study with amiodarone. Amiodarone failed to alter the ease of inducibility in any consistent fashion.

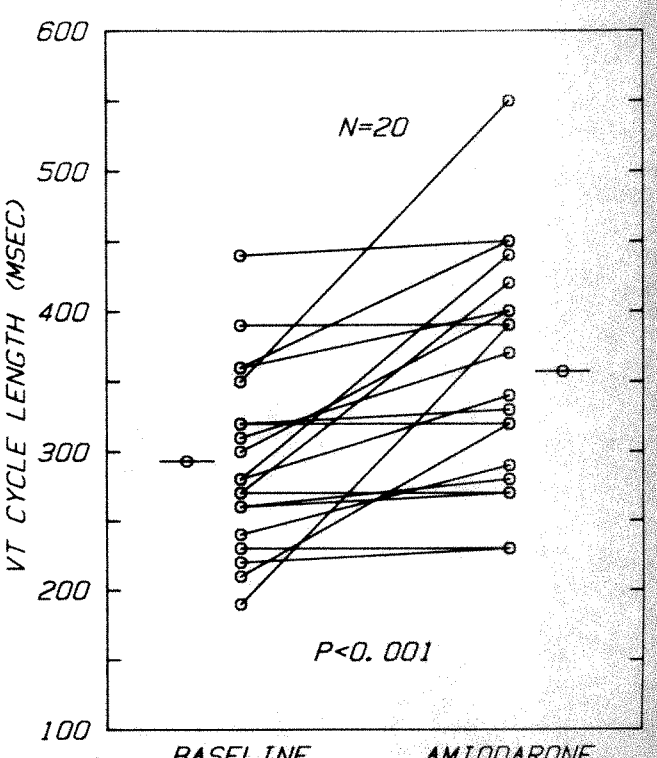
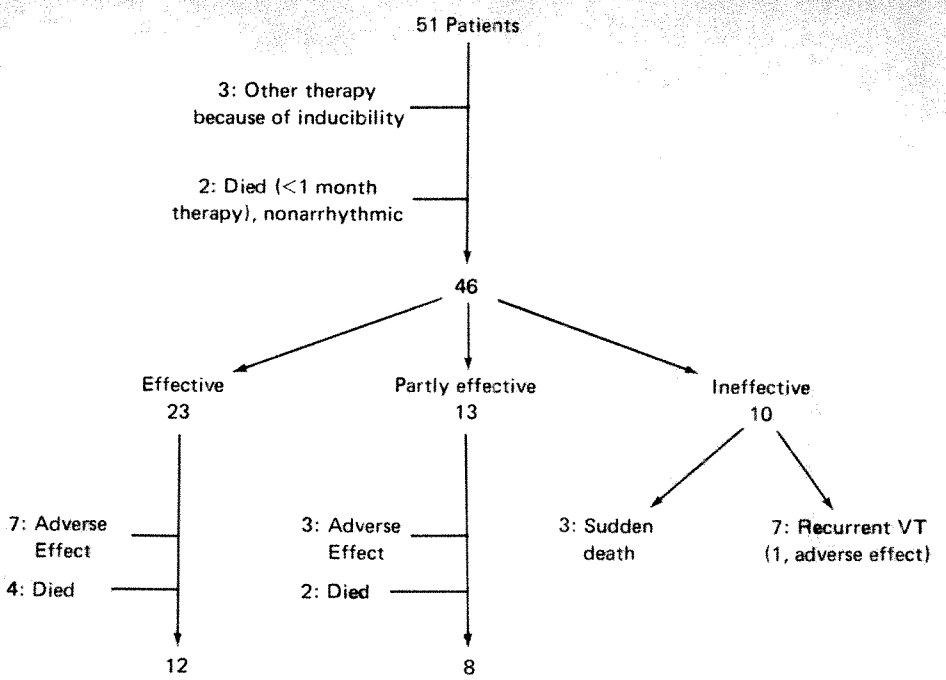


FIGURE 2. Effect of amiodarone on induced VT cycle length in the 20 episodes of VT with similar morphology during the baseline (control) and amiodarone (treatment) study.

TABLE II Clinical Efficacy of Amiodarone



Ineffective group: Amiodarone was ineffective in controlling arrhythmia in 10 of 46 patients (20%). Three of the 10 patients in whom amiodarone was judged ineffective died suddenly. One of these patients (Case 25) was placed on amiodarone therapy because of hemodynamically well-tolerated incessant VT which was controlled with amiodarone and quinidine. This patient had never had cardiac arrest before amiodarone and had tolerated incessant VT for more than 1 week before amiodarone therapy. Furthermore, quinidine therapy was ineffective but well tolerated before amiodarone. He died suddenly 4 months after starting amiodarone in spite of good control of clinical VT. The other 2 patients who died suddenly after 1.5 and 11.5 months of therapy were being treated for paroxysmal sustained VT, but only 1 patient had had a prior cardiac arrest. The latter patient was placed on quinidine in addition to amiodarone because it slowed the rate of induced VT. Quinidine had been well tolerated but ineffective before amiodarone. This patient had no recurrence for the 11.5 months before sudden death. A fourth patient (Case 22) died from infarcted bowel after 5 months of therapy but continued to have recurrent episodes of VT in spite of amiodarone.

Four of the remaining 6 patients in whom amiodarone was judged ineffective had recurrences of VT similar to those observed before amiodarone. One patient had a recurrence after 2 weeks, 2 patients after 1 month, and 1 patient on quinidine and amiodarone after 5 months. This patient was placed on quinidine in addition to amiodarone because it slowed the rate of induced VT. Amiodarone was discontinued because of an adverse effect (pustular psoriasis) in the patient (Case 24) who had a recurrence after 2 weeks.

One of the remaining 2 patients (Case 13) in whom amiodarone was considered ineffective developed rapid VT that degenerated to VF 2 weeks after starting amiodarone. Before amiodarone the patient had had well-tolerated episodes of uniform VT. For this reason the medication was discontinued. Ninety days after starting amiodarone, the other patient (Case 9) had a recurrent syncopal episode which was presumed secondary to ventricular arrhythmia. Amiodarone was considered ineffective and was discontinued.

Results of 24 Hour Holter Monitoring (Table III)

Twenty-four hour Holter monitor recordings were available in 38 patients while on an oral dose of amiodarone or amiodarone plus a type I agent. Amiodarone had been judged (see earlier) effective in 21 of these patients, partly effective in 13, and ineffective in 4. One additional patient had abolition of incessant VT on amiodarone plus quinidine, although a 24 hour Holter monitor recording was not available for analysis. Furthermore, adjustment of amiodarone dosage in the first 25 patients was based upon daily analysis of computerized electrocardiographic telemetry monitoring as detailed in the Methods section.

Twenty patients who had a satisfactory (effective or partly effective) clinical response to amiodarone had 0 to 10 ventricular premature depolarizations (VPDs) on 24 hour Holter monitoring. Thirteen patients with a satisfactory clinical response to amiodarone had 10 to over 1,000 VPDs/24 hours; the remaining patient had episodes of nonsustained VT. Holter recordings were only available in 4 patients who were clinical failures; none had total abolition of ventricular ectopic activity, and 2 had episodes of nonsustained VT.

TABLE III Results of 24 Hour Holter Monitoring (n = 38)*

	VPD/24 Hours				
	0–10	10–100	100–1,000	>1,000	NVST
Effective	11	4	4	2	. . .
Partly effective	9 (8)	1 (1)	1	1	1
Ineffective	. . .	1 (1)	1	. . .	2 (1)

* Numbers in parentheses indicating number of patients receiving type I antiarrhythmic agent in addition to amiodarone. NSVT = nonsustained ventricular tachycardia, 6 beats to 1 minute; VPD = ventricular premature depolarization.

Twenty-four hour Holter monitor recordings during the control state and after amiodarone were available in 14 patients. In the remaining patients, no Holter monitor recording was available off antiarrhythmic medication. Of 3 patients with incessant VT, 1 had less than 10 and 1 had 10 to 100 VPDs per 24 hours, and 1 continued to have episodes of nonsustained VT while on amiodarone. In the 11 remaining patients, the number of VPDs per 24 hours was unchanged or decreased in all instances.

Adverse Effects (Table IV)

All except 2 patients who had a side effect requiring withdrawal of amiodarone were taking 800 mg/day. Major side effects requiring discontinuance of the drug occurred in 11 patients, and minor side effects requiring no change or a decrease in dose occurred in 17 patients (excluding patients with photosensitivity and corneal microdeposits).

Neurologic: Neurologic complications occurred in 5 patients and included peripheral neuropathy in 3 and extrapyramidal symptoms in 2. Four of the 5 patients who exhibited neurologic complications were taking 800 mg/day of amiodarone for 4 to 18 months. In all patients neurologic symptoms improved 1 to 4 months after withdrawal of amiodarone. Of the 2 patients who had extrapyramidal symptoms, 1 had improvement in symptoms after a decrease in dosage from 600 to 400 mg/day. The other patient previously on 800 mg/day of amiodarone was started on 400 mg daily after a 3 week hiatus in therapy. He has done well for 3 months on the lower dose of amiodarone.

Hepatic: Liver toxicity was observed in 10 patients. Its manifestations included clinical evidence of hepatitis in 2 patients and asymptomatic elevations in liver function tests in 8 patients. Most elevations in liver function tests were mild and in the range of 1.5 to 3 times the normal values for alkaline phosphatase and serum glutamic oxalacetic and pyruvic transaminase. Amiodarone was discontinued in the 2 patients with symptoms. In 1 patient all tests returned to normal after several months, while the other patient has remained jaundiced with ascites and elevated liver function tests 6 months after amiodarone withdrawal.

Liver biopsy was performed in 1 of the symptomatic and in 3 of the asymptomatic patients with liver function abnormalities. Attempted liver biopsy was unsuccessful in 1 symptomatic patient because of ascites. In the 1 symptomatic patient and 2 of the asymptomatic patients, biopsy revealed prominent micro- and macrovesicular cytoplasmic fatty infiltration with minimal inflammatory reaction. In the fourth patient with suspected amiodarone liver toxicity, biopsy revealed evidence of probable recent viral hepatitis. All elevations of liver function tests in asymptomatic patients resolved spontaneously or after the amiodarone dosage was decreased.

Dermatologic: Many of the patients exhibited mild to moderate photosensitivity that was controlled with a decrease in sun exposure and the use of sunscreens. One patient had a disabling photosensitivity that was not adequately controlled with sunscreen or a decrease in dosage from 800 to 400 mg daily. In 1 other patient with preexisting active psoriasis, amiodarone was stopped because of pustular psoriasis which developed 2 weeks after amiodarone was started.

Cardiac: Five patients died from congestive heart failure after taking amiodarone for 2 weeks to 7 months. The ejection fraction in these patients ranged from 13

TABLE IV Adverse Effects*

	Instances	Time to Development (mo)
Neurologic		
Peripheral neuropathy	3 (3)	5, 15, 18
Extrapyramidal symptoms	2	3, 4
Liver toxicity		
Symptomatic	2 (2)	6, 10
Asymptomatic (less than 3 times normal, except in 1 patient—5 times normal)	8†	As early as 0.5
Cutaneous		
Photosensitivity, severe	1 (1)	6
Pustular psoriasis	1 (1)	0.5
Increased pigmentation	2	8, 12
Cardiac		
Increased CHF	7	As early as 1
Bradycardia requiring permanent pacemaker	5	As early as 3
Ocular		
Corneal microdeposits	15 of 21‡	As early as 0.5
Photosensitivity	2	6, 12
Thyroid		
Hyperthyroidism	1	8
Pulmonary	5 (4)	5, 8, 9, 10, 10

* Numbers in parentheses indicate the number of patients in whom drug was discontinued because of adverse effect. CHF = congestive heart failure.
† One was probably due to viral hepatitis.
‡ Fifteen of 21 patients with eye examinations on amiodarone for more than 1 month.

to 51 percent before starting amiodarone. In 4 of the 5 patients the ejection fraction was under 30 percent. Two other patients with an ejection fraction of 39 and 45 percent had increased congestive heart failure after amiodarone therapy for 10 and 13 months, respectively. Congestive heart failure improved with conventional therapy and a decrease in amiodarone dosage in these 2 patients.

Five patients required a permanent pacemaker after amiodarone for the following reasons: symptomatic sinus bradycardia in 2, symptomatic slow ventricular rate during atrial fibrillation in 1, heart block in 1, and overdrive suppression of intermittent slow VT with AV sequential pacing in 1.

Ophthalmologic: Asymptomatic corneal microdeposits were observed in 15 of 21 patients who had at least 1 ophthalmologic slit lamp examination while on amiodarone for more than 1 month. Deposits were observed as early as 3 weeks after starting amiodarone. In 2 patients ocular photosensitivity was easily controlled with tinted eyeglasses, and 1 patient developed chromatic aberration in association with very heavy corneal microdeposits.

Thyroid: Clinical hyperthyroidism was observed in 1 patient and required treatment with antithyroid medication.

Pulmonary: Five patients exhibited pulmonary complications. They presented with fever, dyspnea, hypoxia, and infiltrates on chest x-ray after 5 to 10 months of amiodarone therapy. Three patients were taking 800 mg/day and 2 were taking 600 mg/day. Lung biopsy in 4 patients revealed interstitial fibrosis and alveolar exudate, similar to the pathologic findings previously reported.[16] Three patients improved with discontinuation of amiodarone and institution of glucocorticoid therapy. One patient died at another hospital in acute respiratory failure 16 hours after admission with a 2 week history of an upper respiratory tract infection. The remaining patient died from acute respiratory and hemodynamic collapse 1 week after stopping amiodarone therapy.

Discussion

Previous studies: Previous studies performed outside the United States[6,8,11] and recent trials in America[16–19] suggest that amiodarone may be an effective therapeutic agent for control of ventricular arrhythmia. The largest series reported to date[6] using amiodarone for control of ventricular arrhythmia found an 82% response rate. However, in this series of 145 patients with ventricular arrhythmia, only 8 patients had VT or VF associated with ischemic heart disease and left ventricular aneurysm. Six of these 8 patients had what is described as an excellent result during follow-up up to 26 months. A more recent report from the same group of investigators[8] reported an 87% response rate in 23 patients with sustained, recurrent, symptomatic VT followed up for a mean of 24.2 months. Similarly, Heger et al.[16] recently reported a 67% success rate in 40 patients with sustained recurrent VT or VF and 5 patients with nonsustained VT resistant to therapy with other antiarrhythmic agents followed up for a mean of 12.7 months. Thirty patients in this group had ischemic heart disease, but the number of patients with prior documented myocardial infarction and left ventricular aneurysm is not stated.

Electrophysiologic effects: Amiodarone prolongs refractoriness and depresses conduction throughout the heart. Wellens et al.[10] reported that amiodarone prolonged effective refractory periods in the atria, AV node, accessory pathway, and ventricles as well as conduction through the AV node in patients with the Wolff-Parkinson-White syndrome. Heger et al.[16] reported similar electrophysiologic effects on AV nodal conduction and the ventricular effective refractory period in a small group of patients with ventricular arrhythmia, although they noted no prolongation of atrial effective refractory period. They observed a significant increase in sinus cycle length and no significant effects on the H-V interval.

We observed prolonged refractoriness in the atria and ventricles and prolonged conduction through the AV node in our patients. The drug did not affect measures of sinus nodal function, although the sinus cycle length was significantly increased and some patients did develop significant sinus bradycardia. We also observed a small but significant prolongation of the H-V interval, although it was prolonged by 20 ms or more in only 2 patients. One of these 2 patients developed infra-His bundle block during atrial pacing requiring a permanent pacemaker. Some of our patients were on digoxin, propranolol, or both, at the time of control and treatment studies. Although the dosages of these medications were similar at both studies, we cannot exclude the possibility of drug interactions with amiodarone that might have affected the observed results.

Antiarrhythmic effects: In the present study, all patients except 2 had either spontaneous sustained VT or VF. These 2 patients had a history of recurrent syncope with inducible sustained VT during electrophysiologic study. All patients failed multiple trials of antiarrhythmic agents, and combination of agents. Other experimental agents were tried in 14 patients. Forty % of the patients had at least 1 cardiac arrest before starting amiodarone, and 77% required at least 1 cardioversion. Twenty-two of the 39 patients with coronary heart disease had left ventricular aneurysm or had already undergone left ventricular aneurysmectomy. Most patients had evidence of significant left ventricular dysfunction, and the mean ejection fraction in those patients with coronary heart disease was 30 ± 12%. Thus, amiodarone was used more or less as the last resort in this group of patients.

Several investigators have shown that a drug which prevents induction of VT in the electrophysiologic laboratory is associated with short- and long-term arrhythmia suppression.[20–23] Conversely, induction of sustained ventricular tachyarrhythmia during standard drug therapy in the electrophysiologic laboratory usually predicts recurrence on the particular regimen

tested. In contradistinction, a dissociation between arrhythmia induction and clinical response with amiodarone was recently reported.[16] Similarly, we observed that although amiodarone suppressed the induction of ventricular arrhythmia in only 5 of 43 patients, total clinical suppression of arrhythmia was observed in 23 of 46 patients.

The reason for the dissociation between tachycardia induction and clinical response to amiodarone is unknown, although in some patients it may be related to suppression of spontaneous ventricular ectopic activity. In this way amiodarone may be effective in some patients by abolishing the triggers that initiate reentrant ventricular arrhythmias rather than effecting the tachycardia circuit. However, amiodarone must also have some effects on the ventricular arrhythmia circuit as evidenced by its ability to prolong tachycardia cycle length. Furthermore, 14 patients had a good clinical response to amiodarone in spite of continued ventricular ectopic activity on 24 hour Holter monitoring. The reason for achieving arrhythmia control in those patients without abolition of ventricular ectopic activity or noninducibility in the electrophysiologic laboratory is not clear. We cannot exclude the possibility that amiodarone may be effective in some patients by selectively suppressing premature beats that occur at critical coupling intervals responsible for triggering sustained tachyarrhythmia, since we did not measure ventricular premature beat coupling intervals.

Toxic side effects: Amiodarone reportedly has a low incidence of adverse effects.[6,7,18,19] As in earlier reports,[24,25] many of our patients treated with amiodarone developed corneal microdeposits as early as 3 weeks after starting therapy. These deposits were only troublesome in 1 patient. On the other hand, neurologic, hepatic, cutaneous, and thyroid complications were troublesome and necessitated withdrawal of the medication in several instances. In fact, 8 of 21 patients (38%) on 800 mg/day for more than 3 months had side effects severe enough to require discontinuation of the medication. Overall, 10 of 36 patients (28%) with a good clinical response had to have the drug discontinued because of adverse effects.

Neurologic,[26–28] cutaneous,[25,29,30] thyroid,[31,32] and pulmonary[16,33] adverse effects similar to those observed in our patients have been previously noted during amiodarone administration. However, to our knowledge, no prior instances of significant hepatic toxicity have been described except for transient elevations of hepatic enzymes.[16,18] In fact, Plomteux et al.[34] specifically reported good hepatic tolerance to amiodarone in 30 patients treated with 300 to 600 mg/day for 32 weeks. Although in our series most patients with liver function abnormalities were asymptomatic, 2 developed clinical hepatitis necessitating withdrawal of amiodarone treatment. Liver biopsy in 1 symptomatic and 2 asymptomatic patients revealed evidence of fatty infiltration. One patient still had active liver disease 6 months after withdrawal of amiodarone. However, since liver biopsy was not accomplished in this patient, a definite diagnosis of amiodarone toxicity cannot be established. Fortunately, in all instances except this one the adverse effects abated after discontinuation of amiodarone or a decrease in dosage.

One of our patients (Case 13) developed rapid VT associated with cardiac arrest requiring defibrillation 2 weeks after starting amiodarone. The arrhythmia began as a wide complex rapid pleomorphic VT characteristic of torsade de pointes and eventually degenerated to VF. Before amiodarone this patient had recurrent episodes of morphologically uniform and well-tolerated VT. The corrected Q-T interval was mildly prolonged to 0.47 second, and there was no other apparent metabolic derangement to account for the arrhythmia. The amiodarone was withdrawn, and no further recurrence of rapid VT or torsade de pointes was noted. One case of torsade de pointes tachycardia developing with amiodarone was previously reported in the European literature.[35]

Previous studies in animals[36] *and human beings*[37] *have indicated that amiodarone is a potent peripheral vasodilator and may, therefore, have beneficial effects on left ventricular function.* However, amiodarone is also a potent competitive nonselective catecholamine antagonist which might contribute to a worsening of congestive heart failure.[36] Several of our patients had an increase in congestive heart failure while on amiodarone. Since most of the patients in this series had evidence of significant left ventricular dysfunction before amiodarone therapy, it is unclear whether this exacerbation of failure was due to amiodarone or the natural history of the underlying disease. Furthermore, when amiodarone interruption was associated with an improvement in congestive heart failure, it was accompanied by changes in concomitant therapy. Further studies are needed to define the effects of prolonged amiodarone treatment on left ventricular function in patients with significant underlying heart disease.

The development of pulmonary complications on amiodarone has been reported previously and is probably the most troublesome adverse effect.[16,33] Our 5 cases add further evidence that this complication is indeed related to amiodarone therapy. The relationship of amiodarone dosage to the development of pulmonary toxicity is unclear. In 1 patient on amiodarone, 400 mg/day, for 1 month pulmonary toxicity was reported.[33] The patients in our series who developed pulmonary toxicity were taking 600 to 800 mg/day for 5 to 10 months.

The high incidence of adverse effects observed in our population may be related to the high dose employed in some cases. Nevertheless, others have reported an extremely low incidence of side effects using comparable doses.[8,18] The reasons for this discrepancy are unclear.

Conclusions: Amiodarone provided effective or partly effective treatment in 36 of 46 (78%) of our patients with medically and, in some cases, medically and surgically refractory ventricular tachyarrhythmia. It appears that electrophysiologic testing cannot help

guide therapy since in most patients tachycardia remains inducible on amiodarone in spite of good clinical results. However, electrophysiologic testing may be indicated in those patients with rapid, poorly tolerated VT before amiodarone therapy. In these patients electrophysiologic testing on amiodarone might help to determine whether the addition of another antiarrhythmic agent is indicated. The addition of another antiarrhythmic agent might slow the rate of induced VT so that if recurrences occur, they may not be associated with cardiac arrest.

Amiodarone in the doses tested, especially 800 mg/day, was associated with a significant incidence of adverse effects which frequently require a decrease in dosage or even discontinuation of treatment. Based on these results, we believe the long-term treatment with more than 600 mg/day of amiodarone should be avoided.

Further clinical testing of amiodarone is warranted since it provided effective therapy in patients with refractory ventricular tachyarrhythmia. At present, its use should be reserved for patients with medically refractory sustained ventricular tachyarrhythmia. In this group of patients, the potential for adverse effects is acceptable based on a favorable risk-benefit ratio.

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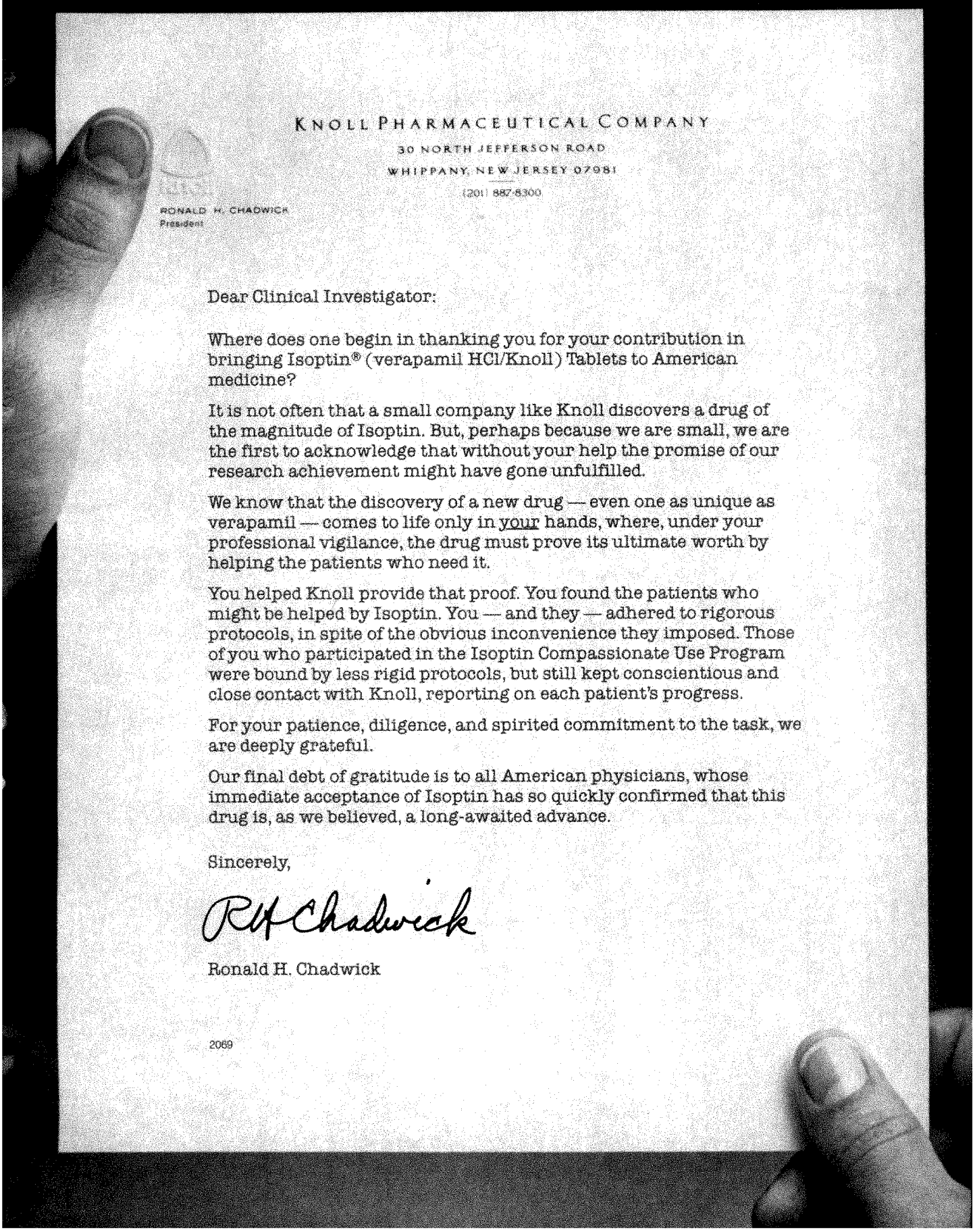
This thank-you letter is too important to be buried in a pile of mail.



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30 NORTH JEFFERSON ROAD

WHIPPANY, NEW JERSEY 07981

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RONALD H. CHADWICK
President

Dear Clinical Investigator:

Where does one begin in thanking you for your contribution in bringing Isoptin® (verapamil HCl/Knoll) Tablets to American medicine?

It is not often that a small company like Knoll discovers a drug of the magnitude of Isoptin. But, perhaps because we are small, we are the first to acknowledge that without your help the promise of our research achievement might have gone unfulfilled.

We know that the discovery of a new drug — even one as unique as verapamil — comes to life only in your hands, where, under your professional vigilance, the drug must prove its ultimate worth by helping the patients who need it.

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For your patience, diligence, and spirited commitment to the task, we are deeply grateful.

Our final debt of gratitude is to all American physicians, whose immediate acceptance of Isoptin has so quickly confirmed that this drug is, as we believed, a long-awaited advance.

Sincerely,

RH Chadwick

Ronald H. Chadwick

2069

CARDIOLOGY: 1982

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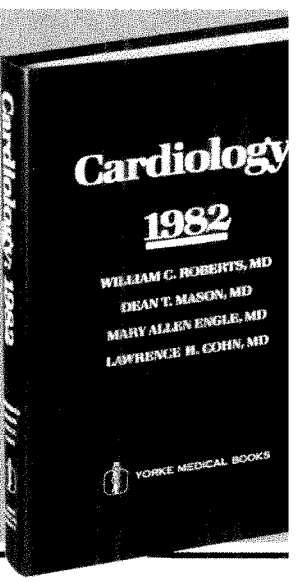
ISBN 0-914316-27-3 approx. 500 pp., illus., April 1982, $45.00 ISSN 0275-0066



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- A review of the year's newest and most important developments in cardiology — **665 papers**
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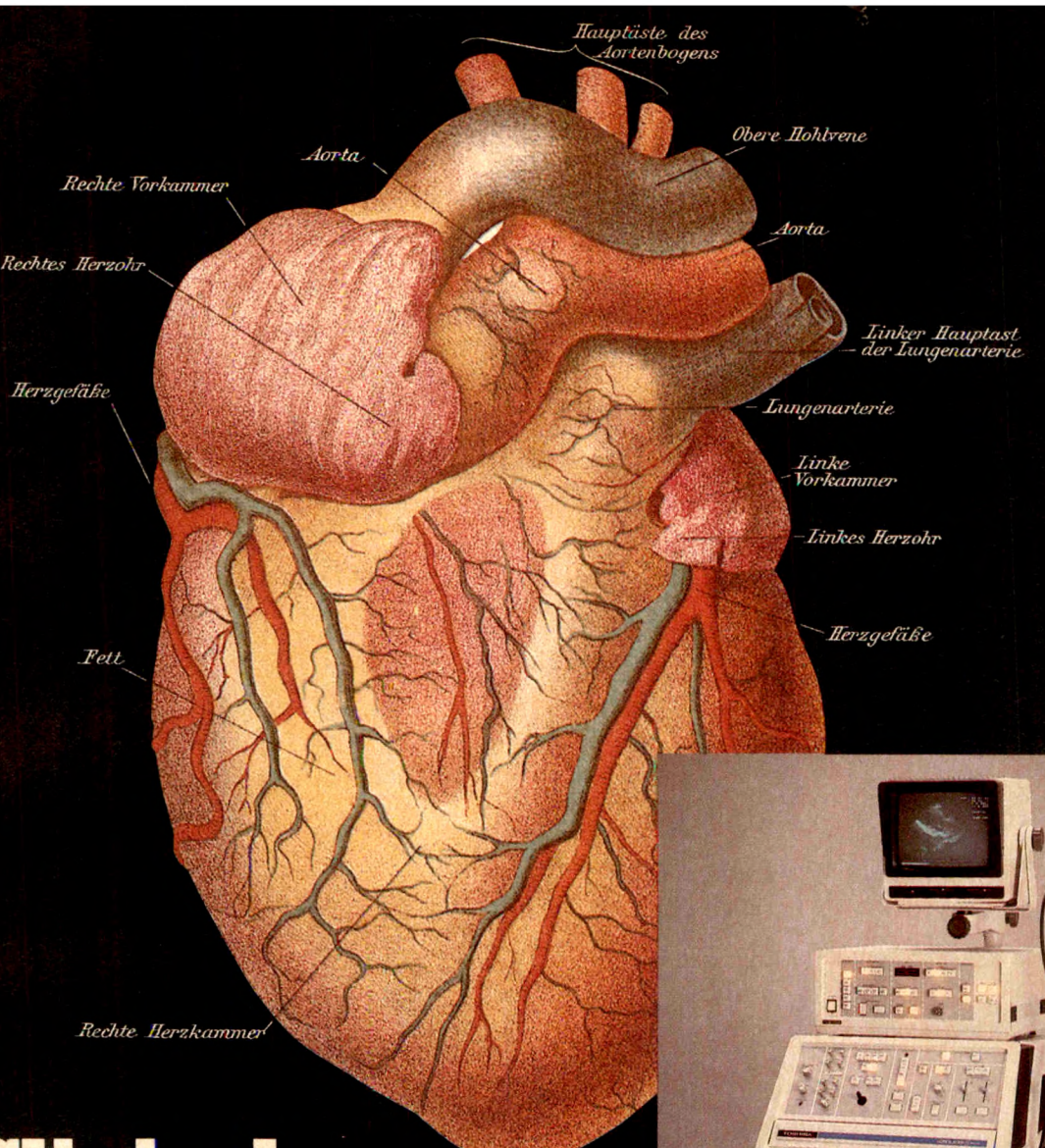

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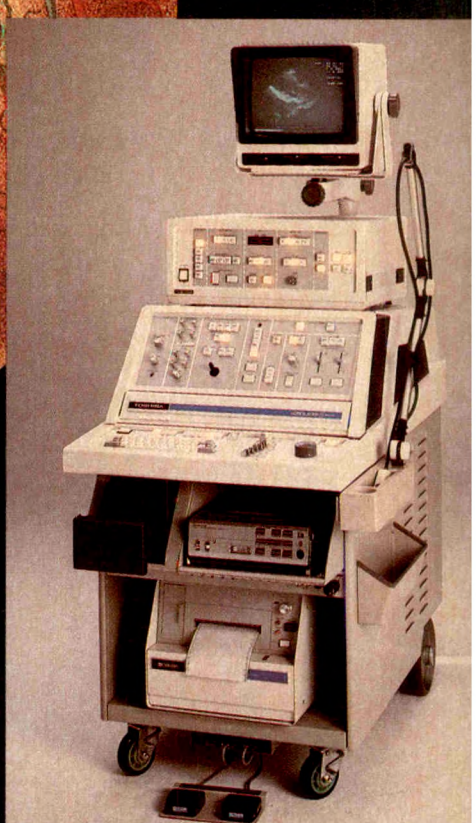

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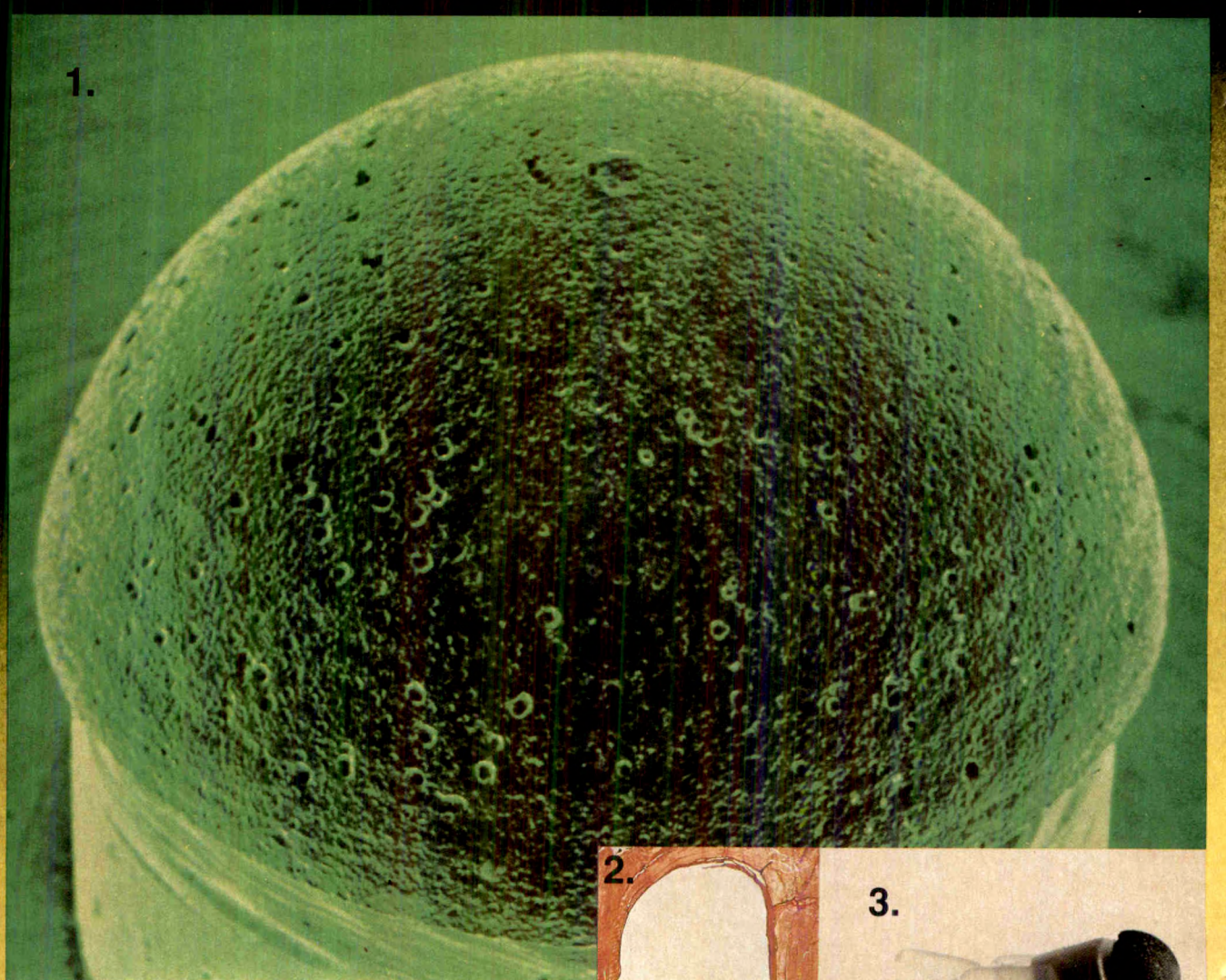

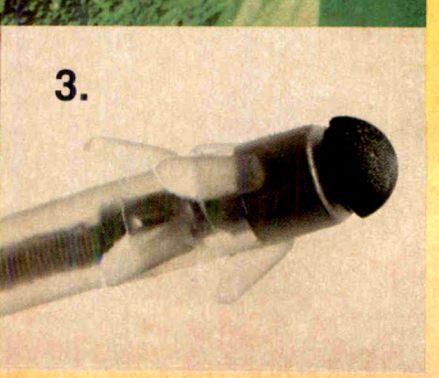

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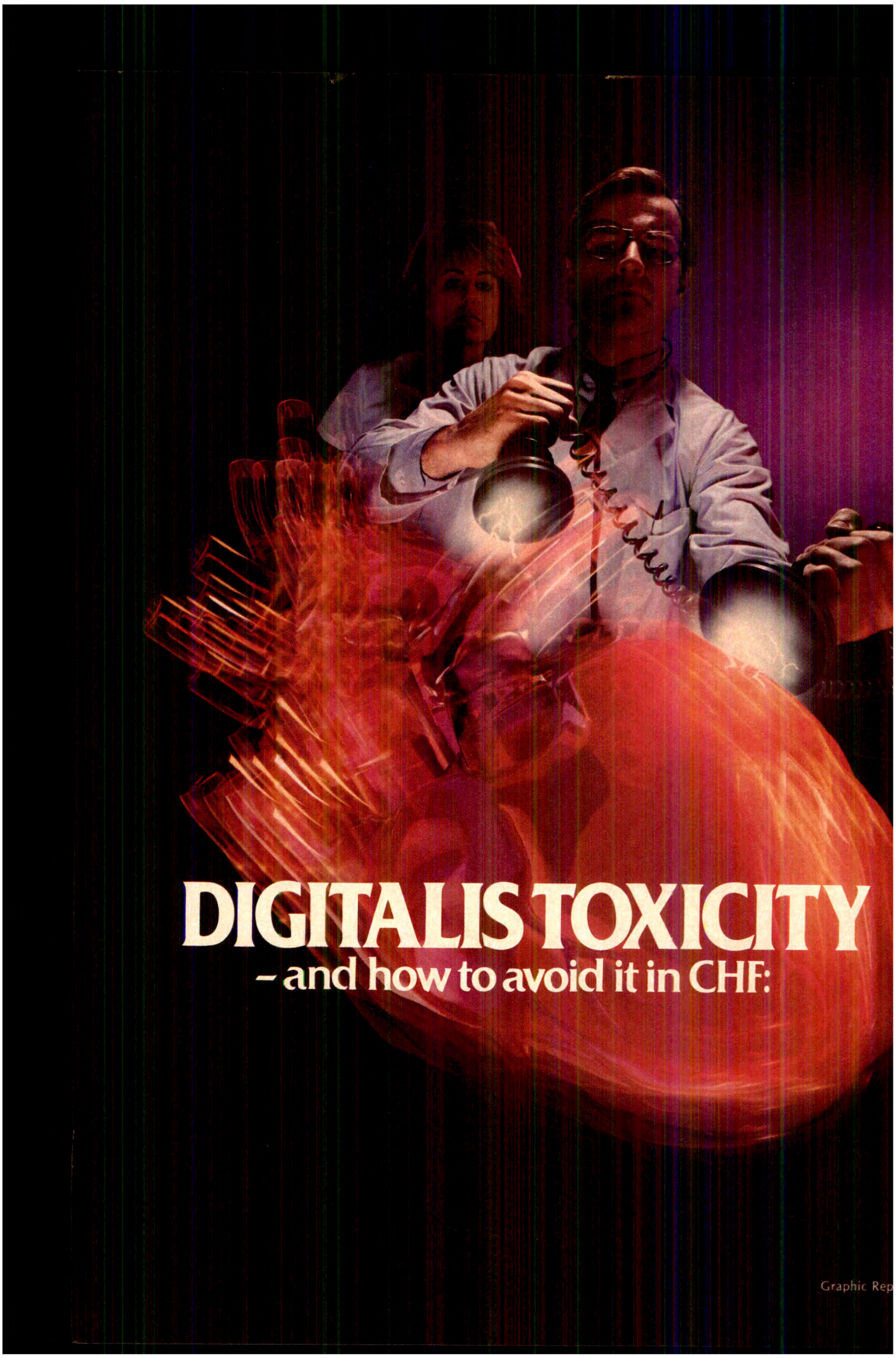
DIGITALIS TOXICITY
– and how to avoid it in CHF:
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But many patients with impaired renal function are particularly vulnerable because their condition may predispose them to a toxic accumulation of digoxin.

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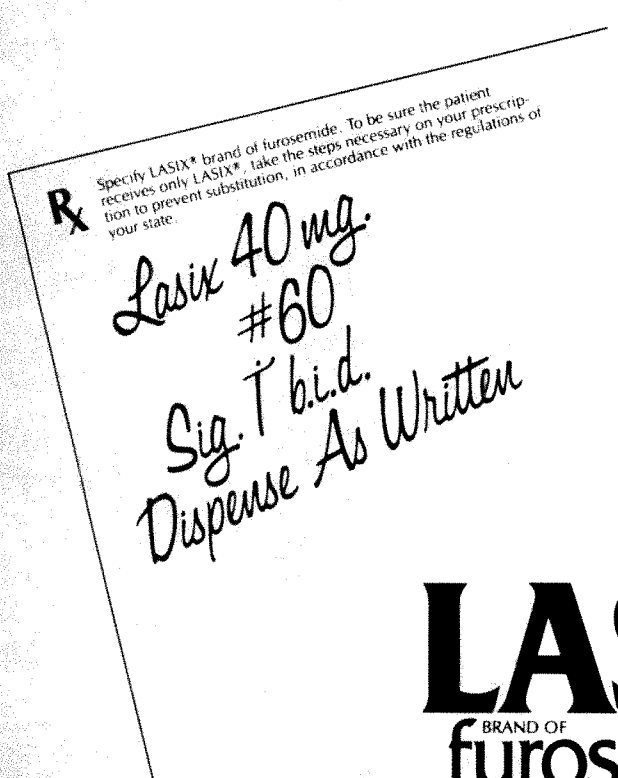
As to the first, the narrow therapeutic-to-toxic range of digitalis is well known and requires no elaboration.



Naturally, increased renal problems necessitate increased vigilance to any signs of toxicity.

Why the patient should be maintained on LASIX®

The second precaution is the unvarying use of a single diuretic for a given patient (consistent with proper potassium balance). Thus, if the choice is LASIX®—as it is in most successfully managed CHF cases—the logic behind it is beyond debate. LASIX® is the only diuretic for CHF whose effectiveness has been confirmed in no fewer than 6,000 published papers...which offers the most complete range of dosage forms and strengths for precise titration.., and is the most widely available brand of furosemide for filling or refilling your prescription anywhere in the United States. In fact, according to a 1980 nationwide survey,[1] office-based physicians affirmed their confidence in LASIX® by naming it as the medication they prescribe most frequently in office practice.

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When you prescribe LASIX®, write the phrase "Do not substitute," or whatever your state requires on the prescription.

If you are in doubt about a particular generic furosemide, call the offices of the Food and Drug Administration's Bureau of Drugs, Consumer and Professional Relations staff at 301-443-1016.

Reference: 1. Koch H: Drugs most frequently used in office-based practice: National Ambulatory Medical Care Survey, 1980, Vital and Health Statistics of the Nat Ctr for Health Statistics, No. 78 (May 12) 1982.

Before prescribing, please consult complete product information, a summary of which appears on the following page.

LASIX®

TABLETS: 20, 40 & 80 mg

BRAND OF furosemide

The diuretic of choice for the digitalized patient.

Lasix® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide) Tablets 20, 40 and 80 mg.

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

PREGNANCY: Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2.4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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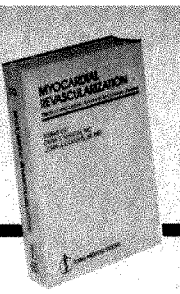

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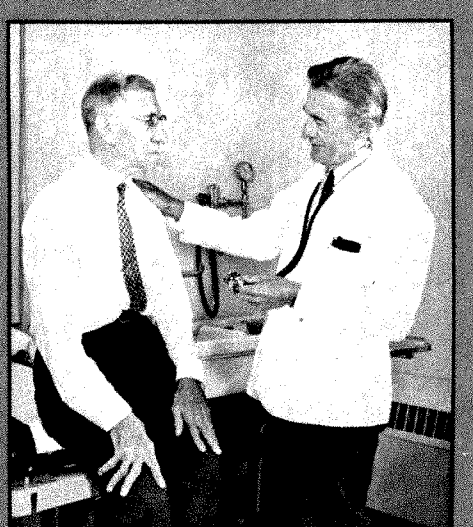

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After more than six years of development and rigorous clinical evaluation, a microcomputer based system called AEGIS™ is now available for ambulatory monitoring.

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Microcomputer Technology

The AEGIS Real Time Analyzer, a powerful 8 bit microcomputer system, combines the recording and analyzing activities in one unit that analyzes each heartbeat in real time, detecting, categorizing and counting arrhythmias as they actually occur. Because the analysis is in real time, the system is able to apply substantially more instructions per QRS than much more powerful computer systems operating at 60 to 240 times real time.

Accurate, consistent arrhythmia detection

AEGIS analyzes arrhythmias detecting departures in rate, rhythm and morphology from each patient's normal reference. The AEGIS computer can find and reference a patient's "normal" beat in less than two minutes even under a wide variety of difficult conditions such as chronic bigeminy, atrial fibrillation and bundle branch block. Furthermore, the "normal" reference beat is continually updated throughout the analysis period to account for changes in the position of the heart due to body movement.

Abnormal morphologies are detected via both feature extraction and template matching. (AEGIS is unique in its use of both methods of analysis.) When deviations exceed specified criteria, a morphology change is noted.

Rate, rhythm and morphology information is then applied to decision algorithms to determine the classification of each specific morphology change.

Overcoming problems caused by artifacts

To overcome the problem of artifacts and interference distorting information, AEGIS utilizes a series of highly refined classification algorithms developed from a data base of several hundred patients with a variety of morphologies, amplitudes and artifacts. A dual channel system, AEGIS also has the unique capability of being able to sense when artifacts are overwhelming the usefulness of information and to switch automatically to the other lead signal for processing.

Decision-making capability

The AEGIS 8 bit microcomputer system is augmented by an analog preprocessor which performs filtering, automatic gain control and QRS detection functions. Thus, the microcomputer has more time and memory available for real time decision making. In fact, AEGIS is able to apply many more computer cycles in this decision making than far more expensive scanner systems operating at high speeds.

Simplification

Because all analysis occurs within the compact 2.2 pound AEGIS Real Time Analyzer, the conventional high-speed scanner is replaced by a simple, automatic playback unit called a Report Generator. The need for a specially trained operator is eliminated.

Also eliminated are the dependence of reports on the qualitative perceptions of individuals and the inaccuracies or inconsistencies that result from operator variability and fatigue.

Advantages to the physician

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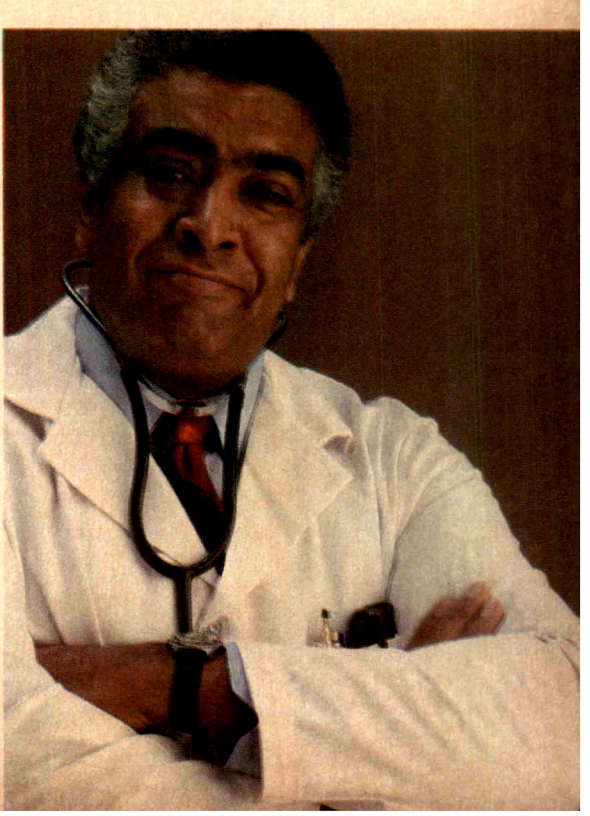

Mead Johnson
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KLOTRIX®
(POTASSIUM CHLORIDE) SLOW-RELEASE TABLETS, 10 mEq

DESCRIPTION KLOTRIX is a film-coated (not enteric-coated) tablet containing 750 mg potassium chloride (equivalent to 10 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS—BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS Hyperkalemia: In patients with impaired mechanisms for excreting potassium administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with potassium-sparing diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. KLOTRIX is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. KLOTRIX should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram and clinical status of patient.

ADVERSE REACTIONS Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose. One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.

Note: KLOTRIX® slow-release tablets must be swallowed whole and never crushed or chewed. Following release of the potassium chloride, the expended wax matrix, which is not absorbed, may be observed in the stool.

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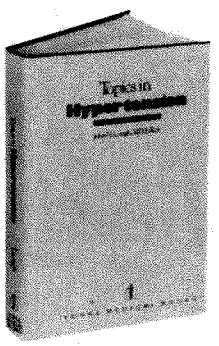

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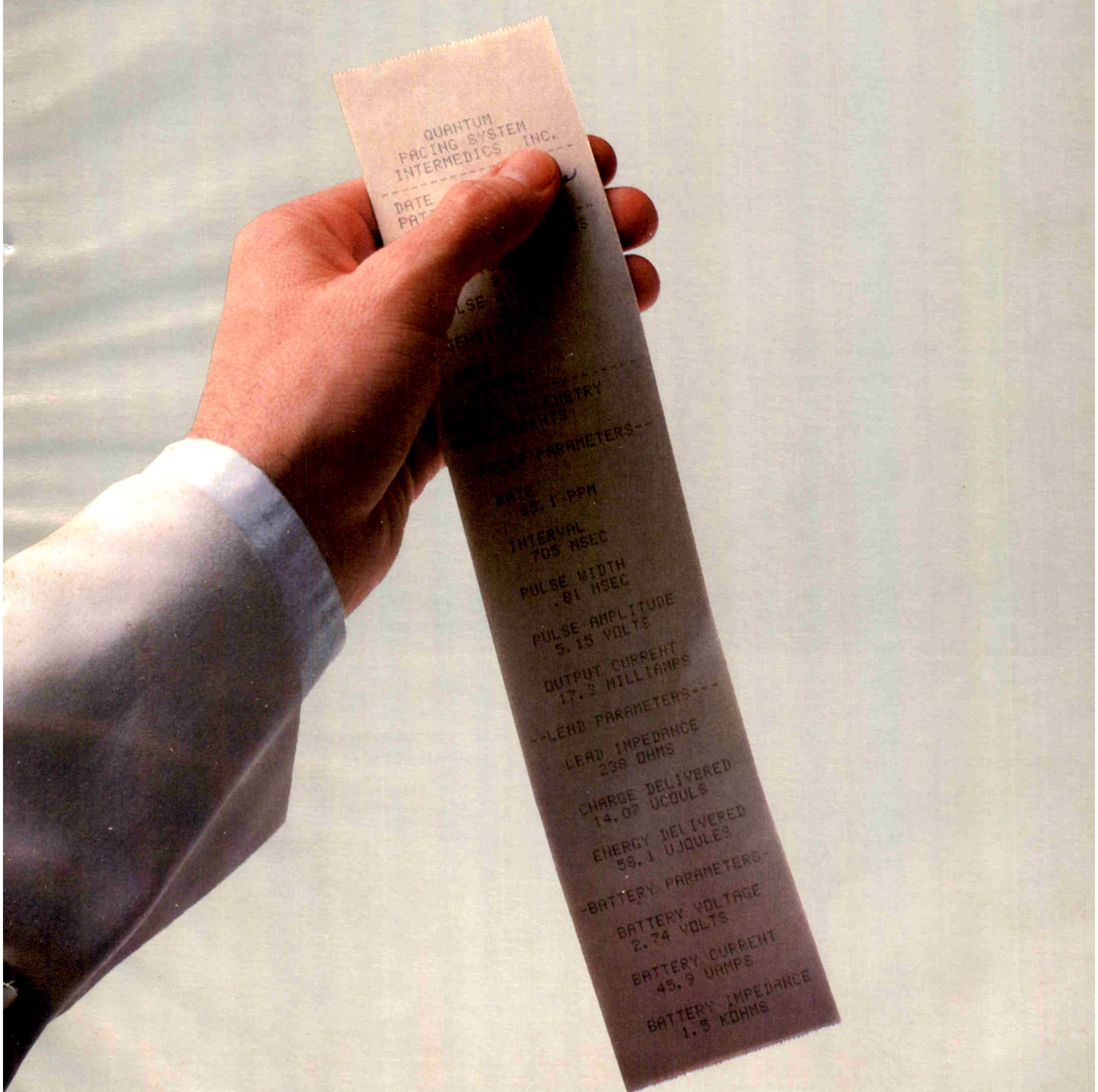

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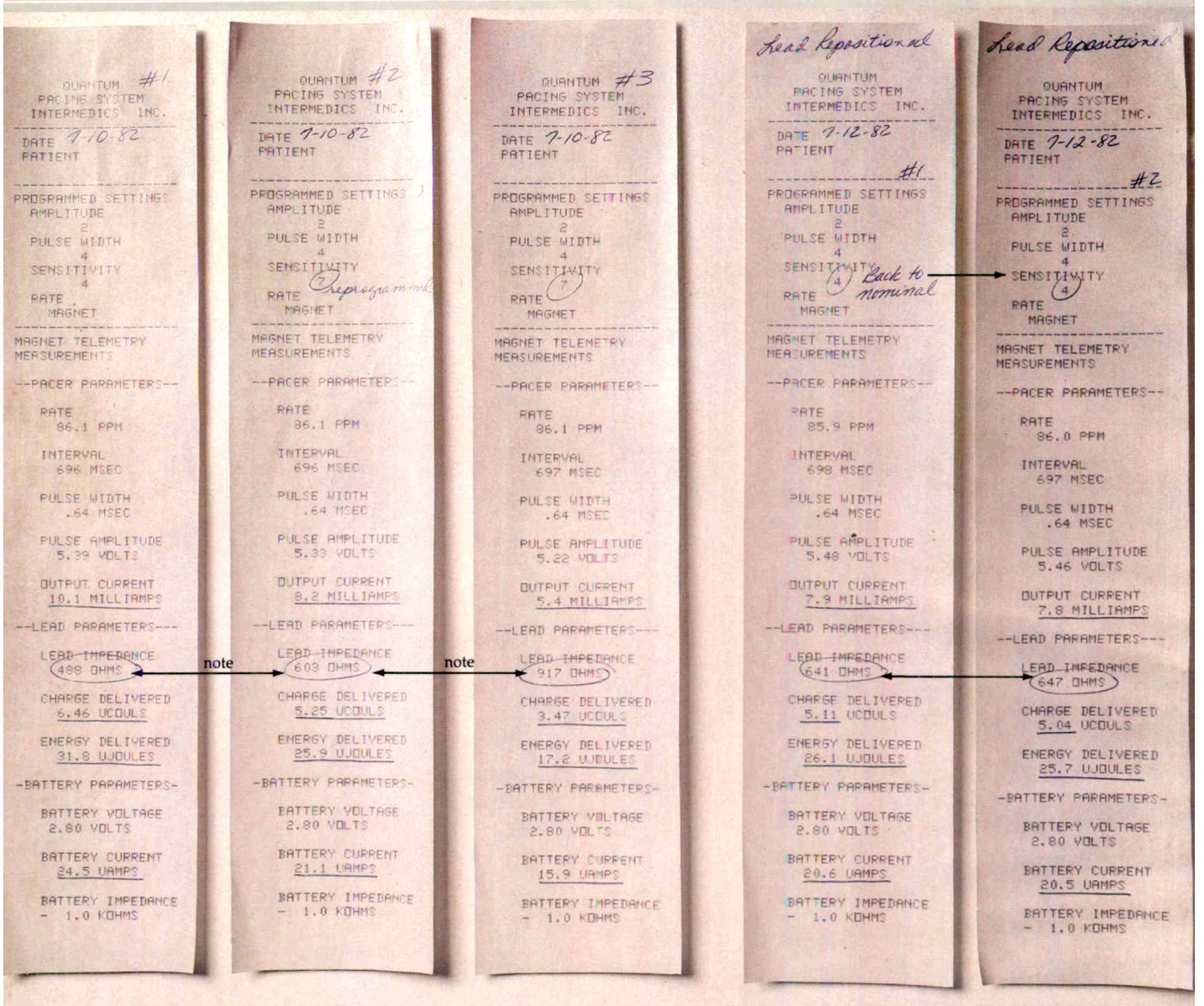

An Actual Case History*

Patient: MALE
Age: 81 YEARS
Diagnosis: HEART BLOCK, BRADYCARDIA WITH EPISODES OF VENTRICULAR TACHYCARDIA
Indication for Pacing: ARRHYTHMIA (BRADYCARDIA) CONTROL

The patient received a Quantum model 253-09 pulse generator with a transvenous unipolar lead. Intra-operative fluoroscopy and threshold testing indicated acceptable lead position.

Eighteen hours post implant, telemetry measurements displayed lead parameters that fluctuated widely, as shown in three successive telemetry printouts. The patient was uncomfortable and while there was no evidence of loss of capture on the EKG, pacing and sensing were irregular. Further investigation and discussion between the cardiologist and implanting surgeon led to a decision to reposition the lead. Repositioning surgery was successful.

Normal pacing and sensing were observed after repositioning. Successive telemetry measurements showed stable lead parameters, verifying that a more satisfactory position had been achieved. The patient was discharged following good post-operative recovery and subsequent telemetry follow-up demonstrated chronic lead stability.

*This actual case history is on record at Intermedics, Inc. For more information, contact the Marketing Dept., Intermedics, Inc.

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Lack of Effectiveness of Oral Mexiletine in Patients With Drug-Refractory Paroxysmal Sustained Ventricular Tachycardia

A Study Utilizing Programmed Stimulation

EDWIN V. PALILEO, MD, WILLIAM WELCH, MD, JULIE HOFF, Pharm D, BORIS STRASBERG, MD, ROBERT A. BAUERNFEIND, MD, STEVEN SWIRYN, MD, ALDO COELHO, MD, and KENNETH M. ROSEN, MD

Recent studies indicate that oral administration of mexiletine is useful in the therapy of recurrent ventricular tachycardia (VT). To further define the clinical usefulness of this drug, mexiletine was administered to 13 men and 4 women with a mean age ± standard deviation of 62 ± 8 years who had drug-refractory paroxysmal sustained VT associated with chronic ischemic heart disease in 14, valvular heart disease in 1, and primary myocardial disease in 1. One patient had no heart disease. All 17 patients had inducible sustained VT during the control electrophysiologic study and during serial electrophysiologic study on conventional drugs. Eleven patients tolerated a mean maximal daily dose of 1,073 ± 149 mg of mexiletine and underwent programmed ventricular stimulation; sustained VT was inducible in 10 patients and nonsustained VT in 1. In 10 patients with inducible sustained VT on mexiletine, the VT cycle length was longer during mexiletine therapy than during control (mean ± standard error of the mean, 342 ± 22 versus 268 ± 14 ms, respectively) ($p < 0.005$). Programmed stimulation was not possible in 1 patient with severe neurologic side effects and in 5 patients with mexiletine-related worsening of ventricular arrhythmia. Seven other patients had severe neurologic or gastrointestinal side effects, necessitating dose reduction in 5. This 47% incidence of noncardiovascular side effects is similar to that in previous reports, but the 29% incidence of arrhythmia potentiation by mexiletine is unexpectedly higher. Limited follow-up reveals recurrence of VT in 3 of 4 patients treated with oral mexiletine on a long-term basis. In conclusion, oral mexiletine does not appear useful in the therapy of patients with drug-refractory, paroxysmal sustained VT. In addition, its use is associated with a high incidence of adverse effects, cardiovascular (arrhythmic) and noncardiovascular, some of which can be serious and life-threatening.

During the last decade, major advances have been made in the understanding of recurrent sustained VT.[1,2] During the last 5 years, various electrophysiologic,[3,4] surgical,[5,6] and pacemaker[7,8] approaches to the therapy of recurrent sustained VT have evolved, reflecting not only advances in understanding, but also the difficulty in managing this clinical problem. The continuing development of multiple new antiarrhythmic drugs reflects major deficiencies in currently available drugs.

From the Section of Cardiology, Department of Medicine, Abraham Lincoln School of Medicine, University of Illinois College of Medicine and West Side Veterans Administration Medical Center, Chicago, Illinois. This study was supported in part by Institutional Training Grant HL 073787 and Research Grants HL 18794 and 23566 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, and by grants from the Eleanor B. Pillsbury Resident Trust Fund and the Bane Estate, Chicago, Illinois. Manuscript received March 9, 1982; revised manuscript received March 10, 1982, accepted May 13, 1982.

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One of these new drugs is mexiletine, a phenethanolamine compound chemically similar to lidocaine and possessing electrophysiologic properties which resemble lidocaine in some actions and quinidine in others.[9,10] Although clinical trials have demonstrated its effectiveness in ventricular arrhythmias associated with a variety of heart diseases,[11,12] its effectiveness in recurrent sustained VT not associated with acute myocardial infarction was not known until recently.[13,14] Ruskin et al.[13] demonstrated its effectiveness as a single drug in 9 patients and as part of a combination regimen in 4 of 25 patients resuscitated from out-of-hospital cardiac arrest due to VT or ventricular fibrillation, utilizing the technique of serial electrophysiologic and pharmacologic testing. The same investigators,[14] utilizing serial electrophysiologic testing, reported that in 17 of 41 patients with recurrent ventricular arrhythmias resistant to conventional drugs, mexiletine suppressed ventricular arrhythmia during acute administration. Encouraged by these reports indicating that mexiletine

is useful in recurrent sustained VT and to further define its clinical usefulness, we systematically evaluated oral mexiletine in a group of patients with paroxysmal sustained VT which was refractory to conventional drugs.

Methods

Study patients: All patients were referred to the University of Illinois Hospital or the West Side Veterans Administration Medical Center for evaluation and management of paroxysmal sustained VT. Criteria for inclusion in the study were as follows: (1) electrocardiographically documented paroxysmal sustained VT; (2) induction of sustained VT during control electrophysiologic study; and (3) demonstration of refractoriness to conventional antiarrhythmic drugs, defined as the continued ability to have electrically inducible or spontaneously occurring VT while on adequate therapy (with therapeutic serum drug levels) with conventional drugs, or the inability to tolerate therapeutic doses of conventional drugs. Patients with recent myocardial infarction (within 6 weeks) were excluded.

Clinical characteristics: The presence or absence as well as the nature and severity of heart disease were evaluated by history, physical examination, chest x-ray, resting and stress electrocardiography, echocardiography, radionuclide angiography, and cardiac catheterization as clinically indicated.

Control electrophysiologic study: These studies were performed with the patients in the nonsedated postabsorptive state, after informed written consent had been obtained and after all antiarrhythmic drugs had been discontinued for at least 5 drug half-lives. Multipolar electrode catheters with a 1 cm interelectrode distance were inserted either percutaneously or through venesection and were positioned at the high lateral right atrium, the right atrioventricular junction at the region of the His bundle, and the apex of the right ventricle. Intracavity bipolar electrograms were filtered between 30 and 500 Hz and displayed simultaneously with surface electrocardiographic leads I, II, III, and V_1 on a multichannel oscilloscope and recorded at paper speeds of 100 and 250 mm/s utilizing a fiberoptic photographic recorder (Electronics for Medicine, Minneapolis). These data were also stored on magnetic tape utilizing a multichannel, frequency modulation magnetic tape recorder (Honeywell-Electronics for Medicine) for future retrieval.

Cardiac stimulation was provided by an optically isolated, digital programmable stimulator (M. Bloom, Narbeth, Pennsylvania) which delivered rectangular pulses of 2 ms duration and current strength of approximately twice diastolic threshold.

The following stimulation protocol was used in all studies: (1) atrial incremental pacing from a rate just above the sinus rate to a rate producing second-degree atrioventricular block; (2) atrial extrastimulus testing coupled to sinus rhythm and to multiple atrial driven rhythms at cycle lengths shorter than sinus cycle length; (3) a single ventricular extrastimulus coupled to a ventricular driven rhythm at cycle lengths of 450 to 600 ms; (4) double ventricular extrastimuli (V_1–V_2–V_3) coupled to a ventricular driven rhythm at cycle lengths of 450 to 600 ms; (5) bursts of rapid ventricular pacing from rates of 120 to 250 beats/min.

These pacing modalities were performed in sequence until VT was induced, ventricular refractoriness was reached, or the maximal pacing rate was achieved. When induced VT was hemodynamically stable, termination by the extrastimulus technique was attempted. Otherwise, bursts of rapid ventricular pacing at progressively increasing rates above the tachycardia rate was utilized for termination of tachycardia. In patients who exhibited hemodynamic deterioration from prolonged VT due to difficult termination, acceleration of VT during attempts at termination, or deterioration to ventricular flutter or fibrillation, external direct current cardioversion was performed immediately. Use of electrical cardioversion or extreme difficulty in pacing conversion of induced VT precluded completion of the stimulation protocol on any given day.

Serial electrophysiologic testing: When sustained VT could be reliably induced in the control state, a catheter introduced from an arm vein was left indwelling with the distal pair of electrodes located at the apex of the right ventricle. The ventricular stimulation protocol was then repeated after intravenous loading with procainamide (1.0 to 1.5 g total) on the first day and after 4 oral doses of quinidine sulfate (1,600 mg total) and disopyramide phosphate (1,200 mg total) on the second and third days of the serial study, respectively.

Drug responses were defined as successful if sustained VT was not inducible or was converted to nonsustained VT. A response was unsuccessful if sustained VT was still inducible on the drug. An unsuccessful but favorable response was defined as inducible sustained VT, with a significant increase in the tachycardia cycle length associated with a stable hemodynamic state and allowing pacing termination of the tachycardia. Sustained VT was defined as VT lasting longer than 30 seconds and requiring electrical or pharmacologic intervention for termination. Nonsustained VT was defined as VT that spontaneously terminated after 5 beats and before 30 seconds.

Mexiletine protocol: After demonstration of refractoriness to conventional drugs, oral mexiletine was administered at a dose of 200 mg every 8 hours on the first day. If well tolerated, the dose was increased to 300 mg every 8 hours on the second day, and to 400 mg every 8 hours on the third day. In patients who had intolerable neurologic side effects, the dose was reduced until the side effects disappeared or were decreased to tolerable severity. In patients who exhibited a definite worsening of VT before the scheduled electrophysiologic testing, the drug was discontinued and no further testing was carried out. In patients who had no worsening of VT and who tolerated the drug well (in some, after dose reduction), programmed ventricular stimulation was performed while the patient was receiving the highest tolerated dose of mexiletine. In most patients the insertion of a new electrode catheter for testing mexiletine was necessary.

Chronic mexiletine therapy: In patients demonstrating an unsuccessful response to mexiletine, other therapeutic modalities were pursued. In patients demonstrating a successful response to mexiletine, chronic therapy was instituted. In some patients in whom an unsuccessful but favorable response to mexiletine was demonstrated and in whom there were no better therapeutic alternatives, chronic oral mexiletine therapy was also instituted. The dosage used for long-term therapy was identical to the tested dosage for each patient.

Follow-up: Patients on chronic oral mexiletine therapy were followed up in an outpatient arrhythmia clinic on a periodic basis, utilizing repeated ambulatory electrocardiographic recording or transtelephonic transmitters to monitor recurrence of VT.

Analysis of data: A standard Student's t test was used to test the significance of groups of paired data.

TABLE I Clinical Characteristics

Case	Age (yr) & Sex	Diagnosis	Cardio-megaly	WMA	LVEF	Arrhythmia	Cardio-version
1	67M	CIHD	+	+	0.31	VT	+
2	64M	CIHD	+	+	0.25	VT	−
3	70M	CIHD	−	+	0.24	VT	−
4	61M	CIHD	+	+	0.23	VT	−
5	72M	CIHD	+	+	0.24	VT	+
6	55M	CIHD	−	+	0.34	VT	+
7	51F	PMD	+	+	0.44	VT	+
8	51F	VHD	+	+	0.51	VT	+
9	74F	CIHD	+	+	0.28	VT	−
10	57M	CIHD	+	+	0.37	VT	+
11	57M	CIHD	+	+	0.37	VT	−
12	67M	CIHD	−	+	0.35	VT	+
13	66M	CIHD	+	+	0.22	VT	+
14	54M	No OHD	−	−	0.55	VT	−
15	65M	CIHD	+	+	0.30	VT	+
16	75F	CIHD	+	+	0.10	VT	+
17	56M	CIHD	+	+	0.15	VT	−

CIHD = chronic ischemic heart disease; LVEF = left ventricular ejection fraction; OHD = organic heart disease; PMD = primary myocardial disease; VHD = valvular heart disease; VT = ventricular tachycardia; WMA = wall motion abnormality.

Results

Seventeen patients satisfied all inclusion criteria (Table I). There were 13 men and 4 women, aged 51 to 75 years (mean 62 ± 8). (Results are reported as mean ± standard deviation unless stated otherwise.) Sixteen patients had organic heart disease (14 chronic ischemic heart disease, 1 valvular heart disease, and 1 primary cardiomyopathy). One patient had no evidence of structural heart disease. All 16 patients with organic heart disease demonstrated left ventricular wall motion abnormalities on contrast angiography (13 patients), radionuclide angiography (9 patients), or both. Left ventricular ejection fraction ranged from 0.10 to 0.51 (mean 0.29 ± 0.10). In 10 patients with ischemic heart disease who underwent coronary arteriography, significant stenosis (greater than 50 percent narrowing of luminal diameter) was demonstrated in 2 to 3 coronary arteries per patient (mean 2.8 ± 0.4).

Ventricular tachycardia necessitated hospitalization in all patients and required external direct current

TABLE II Electrophysiologic Characteristics

	Control Study				Study on Mexiletine					
Case	Inducible Rhythm	VTCL (ms)	Initiation	Termination	Inducible Rhythm	VTCL (ms)	Initiation	Termination	Dose (mg/day)	Side Effects
1	Sus. VT	300	V_1 V_2 V_3	RVP	Sus. VT	400	RVP	RVP	1,200	...
2*	Sus. VT	300	V_1 V_2 V_3	CV	Sus. VT	350	V_1 V_2 V_3	RVP	1,200	Tremors
3	Sus. VT	200	V_1 V_2 V_3	CV	Sus. VT	390	V_1 V_2 V_3	CV	1,000	Agitation
4	Sus. VT	250	RVP	CV	Sus. VT	260	V_1 V_2 V_3	RVP	1,200	Depersonal-ization
5	Sus. VT	350	V_1 V_2	RVP	NT	...	...	...	400	Torsade de Pointes
6	Sus. VT	400	V_1 V_2 V_3	RVP	NT	...	...	...	900	Spont. VT
7	Sus. VT	280	V_1 V_2 V_3	RVP	NT	...	...	...	400	Spont. VT
8*	Sus. VT	290	V_1 V_2 V_3	CV	Sus. VT	340	V_1 V_2 V_3	RVP	900	Tinnitus, nystagmus
9	Sus. VT	240	V_1 V_2 V_3	CV	NT	...	...	...	600	Weakness, lassitude
10	Sus. VT	270	RVP	CV	Sus. VT	365	V_1 V_2 V_3	RVP	900	Ataxia
11	Sus. VT	370	RVP	RVP	NT	...	...	...	900	Spont. VT
12	Sus. VT	220	V_1 V_2 V_3	RVP	Sus. VT	260	V_1 V_2 V_3	CV	900	Epigastric burning
13*	Sus. VT	350	V_1 V_2 V_3	RVP	Sus. VT	470	V_1 V_2	S_2 S_3	1,200	...
14	Sus. VT	260	V_1 V_2 V_3	CV	Sus. VT	330	V_1 V_2 V_3	RVP	1,200	...
15*	Sus. VT	330	V_1 V_2 V_3	RVP	NSVT	300	RVP	Spont.	1,200	Dizziness
16	Sus. VT	300	RVP	S_2 S_3	NT	...	...	...	200	Spont. VT
17	Sus. VT	240	V_1 V_2 V_3	CV	Sus. VT	250	V_1 V_2 V_3	RVP	900	...

* Patients who received long-term treatment with oral mexiletine.

CV = cardioversion; NSVT = nonsustained ventricular tachycardia; NT = not tested; RVP = bursts of rapid ventricular pacing; S_2 S_3 = double premature stimulation; Spont. = spontaneous; Sus. = sustained; V_1 V_2 = single extrastimulus; V_1 V_2 V_3 = double extrastimulus; VTCL = ventricular tachycardia cycle length.

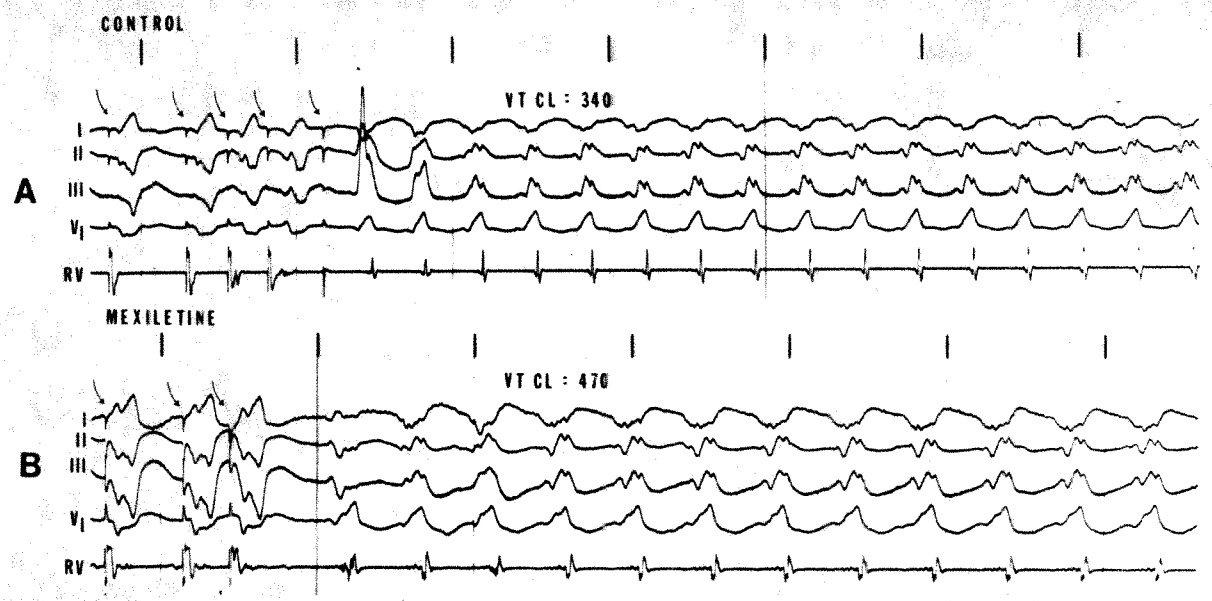

FIGURE 1. An unsuccessful response to mexiletine therapy. Electrocardiographic leads I, II, III, and V_1 and right ventricular electrograms (RV) are shown. VT CL = ventricular tachycardia cycle length. **Arrows** indicate ventricular pacing spikes. **Panel A,** during control study the right ventricle is paced for 8 beats at a cycle length of 500 ms, followed by ventricular extrastimuli at an S_1–S_2 interval of 270 ms, S_2–S_3 of 260 ms, and S_3–S_4 of 300 ms. (The third extrastimulus failed to capture the ventricle.) Sustained VT is induced at a cycle length of 340 ms. **Panel B,** during mexiletine therapy at a total daily dose of 1,200 mg, the right ventricle is paced at a cycle length of 500 ms. After an extrastimulus at an S_1–S_2 interval of 300 ms, sustained VT at a cycle length of 470 ms is induced. Time lines are at 1 second intervals.

cardioversion for termination in 10. The cycle length of spontaneously occurring VT was 275 to 462 ms (mean 359 ± 50) (heart rates 130 to 220 beats/min, mean 167 ± 27).

Control electrophysiologic study (Table II): All patients had inducible sustained VT during the control electrophysiologic study (by study design). VT was induced by double ventricular extrastimulation in 13 patients and by rapid ventricular pacing in 4. Termination was by premature stimulation in 1, by bursts of rapid ventricular pacing in 8, and by external direct current cardioversion in 8. The cycle length of induced VT was 200 to 400 ms (mean 291 ± 55).

Serial electrophysiologic study: All patients underwent serial electrophysiologic testing with conventional drugs, and some patients with other investigational drugs, before mexiletine therapy. These studies demonstrated unsuccessful responses in 3 to 6 separately tested drugs per patient (mean 4 ± 1 drugs per patient) (by study design).

Mexiletine therapy (Table II): Oral mexiletine was administered according to the protocol, with an achieved maximal tolerated daily dose of 900 to 1,200 mg (mean 1,073 ± 149) in 11 patients, allowing evaluation by programmed ventricular stimulation after 1 to 9 days (mean 4 ± 2) of mexiletine therapy. In 6 patients, mexiletine could not be tested by the programmed ventricular stimulation technique (see later). Programmed ventricular stimulation during mexiletine therapy in 11 patients resulted in induction of sustained VT in 10 patients (Fig. 1) and nonsustained VT in one (Fig. 2). Induction was by single and double ventricular extrastimulation in 9 and rapid ventricular pacing in 2. Termination was spontaneous in 1 (the patient with nonsustained VT on mexiletine therapy), by premature stimulation in 1, by bursts of rapid ventricular pacing in 7, and by external direct current cardioversion in 2 patients. In 10 patients with an unsuccessful response to mexiletine, the cycle length of induced VT while on mexiletine was 250 to 470 ms (mean ± standard error of the mean [SEM] 342 ± 22). This was significantly longer than the cycle length of induced VT during the control state, which was 200 to 300 ms (mean ± SEM 268 ± 14) ($p < 0.005$) (Fig. 3). This increase in the tachycardia cycle length allowed termination of pacing in most patients and reduced the necessity for external direct current cardioversion from 7 occasions during the control study to 2 occasions during the mexiletine study.

Mexiletine side effects (Table II): In 6 of the 17 patients, programmed ventricular stimulation during mexiletine therapy was not possible. In 1 patient, mexiletine administration was stopped because of intolerable neurologic side effects after two 200 mg doses. In 5 patients (29 percent), worsening of VT during mexiletine therapy prevented further administration. Sustained VT occurred spontaneously after 6 days of therapy at 900 mg/day in the first patient, and after 2 days at 900 mg/day in the second. The third patient had spontaneous VT requiring external direct current cardioversion after two 200 mg doses of mexiletine, while the fourth patient had multiple episodes of sustained VT requiring repeated pacing conversion and external direct current cardioversion after two 100 mg doses (the

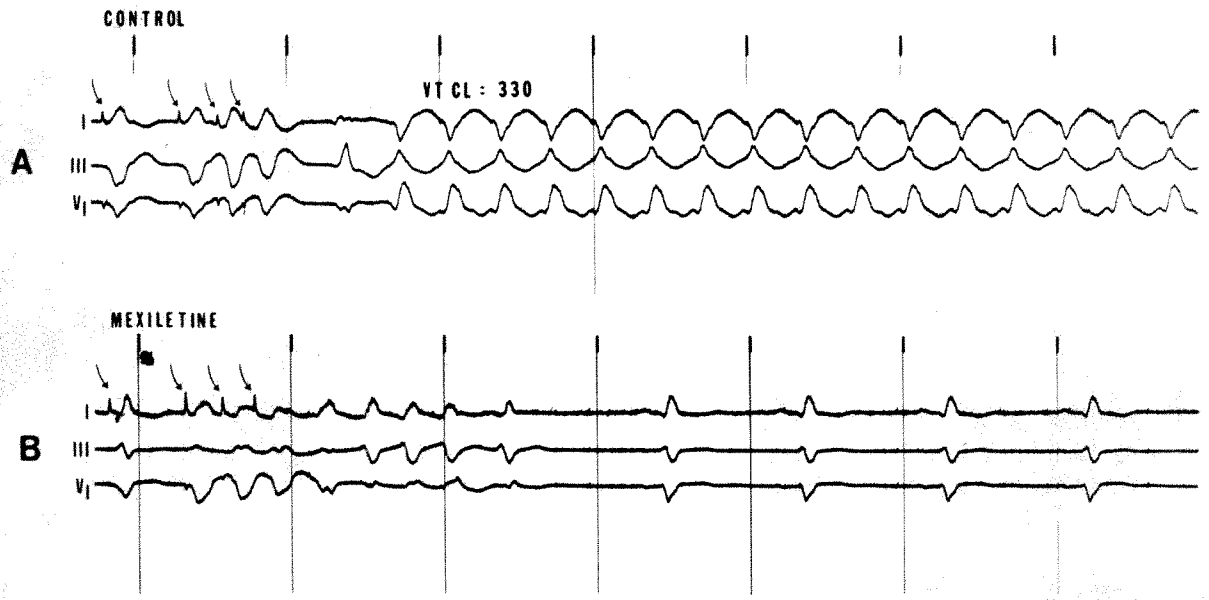

FIGURE 2. A successful response to mexiletine. Arrangement, abbreviations, and symbols as in Figure 1. **Panel A,** during control study the right ventricle is paced for 8 beats at a cycle length of 500 ms, followed by 2 extrastimuli at an S_1–S_2 interval of 250 ms and an S_2–S_3 of 170 ms. Sustained VT is induced at a cycle length of 330 ms. **Panel B,** during mexiletine therapy at a total daily dose of 1,200 mg, the right ventricle is paced at a cycle length of 500 ms followed by 2 extrastimuli at an S_1–S_2 interval of 240 ms and S_2–S_3 of 210 ms. A maximum of 5 beats of nonsustained VT is induced.

lower initial dose in this patient reflects severe adverse experience with previous antiarrhythmic therapy).

In the fifth patient, torsade de pointes was observed for the first time after two 200 mg doses of mexiletine, requiring multiple external direct current cardioversion (Fig. 4).

In each of these 5 patients, the change in pattern of ventricular dysrhythmia was striking, suggesting that mexiletine potentiated VT. These were considered serious and life-threatening adverse effects of mexiletine therapy. In 7 other patients, less serious but incapacitating side effects (neurologic in 6 and gastrointestinal in 1) were observed. Reduction of the mexiletine dose was necessary before serial electrophysiologic testing in 5 of these patients.

Follow-up: In 13 patients, alternative forms of therapy were pursued. The patient who had a successful response to mexiletine was discharged on chronic oral mexiletine therapy at the tested dose. After 2 weeks of therapy, spontaneous sustained VT recurred, requiring hospitalization and external direct current cardioversion. This patient eventually underwent ventricular aneurysmectomy and endocardial resection.

In three patients who did not have other alternate therapy, and who demonstrated an unsuccessful but favorable response to mexiletine, chronic mexiletine therapy was instituted at the tested dose. After 6 to 15 months (mean 10 ± 5) of follow up, one patient has done well without any recurrence (6 months) while two have had multiple recurrence of sustained and usually self-terminating VT, within one to 16 weeks of therapy. Both patients have required hospitalization for recurrent VT.

Discussion

Significant advances in understanding recurrent sustained VT have been made in the last decade.[1,2] Although various electrophysiologic and pharmacologic,[3,4] surgical,[5,6] and pacemaker[7,8] approaches have evolved in the last 5 years, the therapy of recurrent VT remains

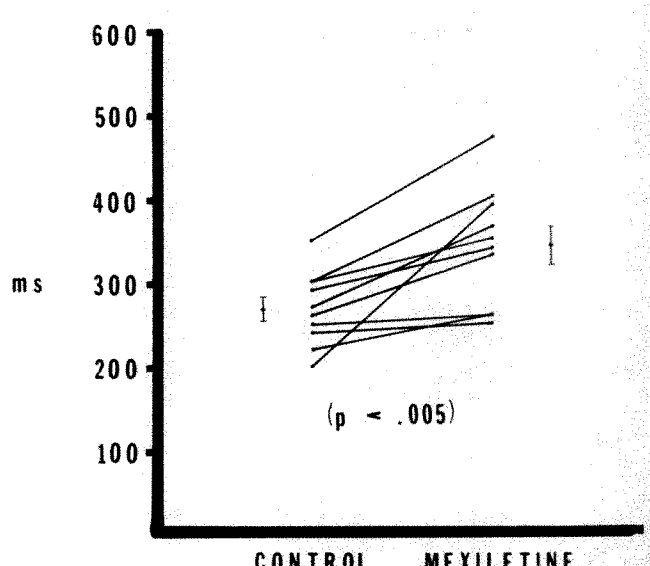

FIGURE 3. Effect of mexiletine on induced VT cycle length in 10 patients with an unsuccessful response to mexiletine. Tachycardia cycle lengths are plotted during control and mexiletine studies in individual patients. Each patient is represented by **solid circles connected by a straight line.** Group mean values are shown on the left for control and on the right for mexiletine tachycardia cycle length.

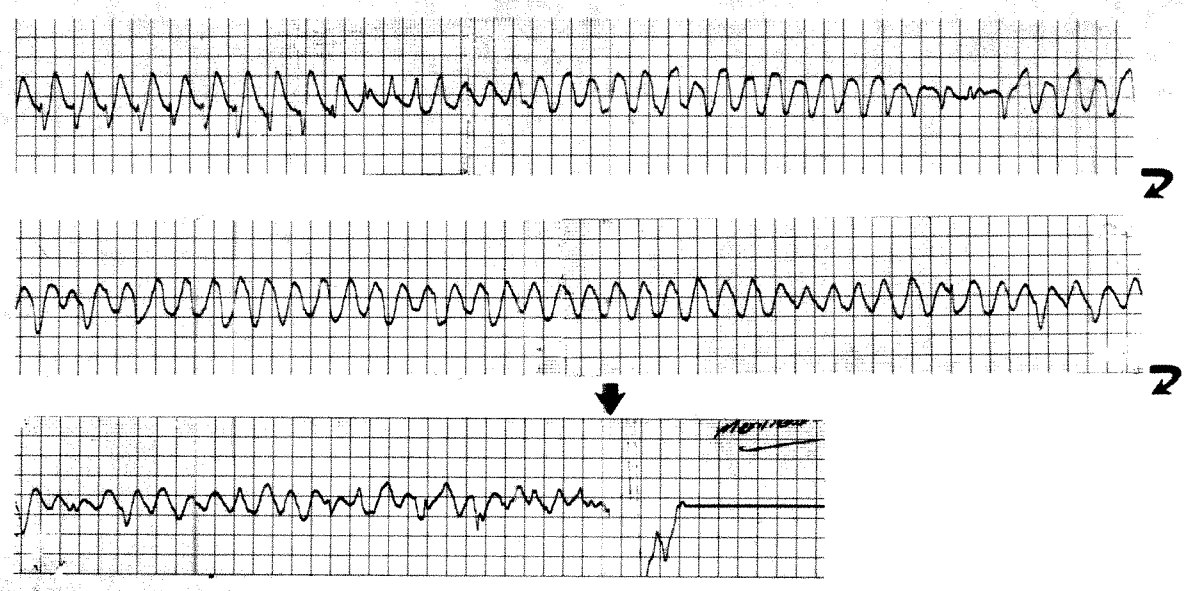

FIGURE 4. Spontaneous ventricular dysrhythmia during mexiletine therapy. Continuous electrocardiographic monitor strip of 1 of several episodes showing initial monomorphic VT converting to polymorphic VT (torsade de pointes) and deteriorating to ventricular fibrillation terminated by external direct current countershock (**bold vertical arrow**). (Discontinuity of the electrocardiographic paper is an artifact owing to the inability of the strip recorder to print continuously for longer than 6 seconds. The **straight line** after cardioversion reflects the inability of the monitor to respond to electrical signals immediately after cardioversion.)

difficult and frustrating. The continuing development of new antiarrhythmic drugs reflects the deficiencies of the currently available drugs.

One of these new drugs is mexiletine, a phenethanolamine compound chemically similar to lidocaine and possessing electrophysiologic properties resembling those of lidocaine in some aspects and quinidine in others.[9,10] Clinical trials have demonstrated its effectiveness in ventricular arrhythmias associated with various forms of heart disease when administrated parenterally or orally.[11,12] More recently, reports indicate that mexiletine may be a very useful antiarrhythmic agent in patients with recurrent ventricular arrhythmias, including patients demonstrating resistance to conventional antiarrhythmic drugs.[13,14]

Ruskin et al.,[13] in a study of 35 patients with out-of-hospital cardiac arrest due to VT or fibrillation, demonstrated inducible ventricular arrhythmia in the electrophysiology laboratory. They found mexiletine an effective drug in 9 patients when used as a single agent and in 4 patients when used in combination with other drugs. The same investigators,[14] in a study of 41 patients with recurrent ventricular arrhythmias resistant to conventional drugs, identified 17 patients in whom mexiletine suppressed ventricular arrhythmia during an acute drug trial utilizing electrophysiologic testing.

In the present study, we evaluated 17 patients with recurrent sustained VT who had inducible sustained VT during control electrophysiologic study and were found refractory to conventional antiarrhythmic drugs. We found that mexiletine failed to prevent the induction of sustained VT by programmed ventricular stimulation in 10 of 11 patients. Previous studies[3,4] have shown that this acute drug trial failure predicts the failure of long-term antiarrhythmic drug therapy in providing prophylaxis against recurrence of VT. In 5 of 17 patients, spontaneous recurrence and worsening of VT during mexiletine therapy indicated drug failure and obviated further electrophysiologic evaluation of mexiletine. In 1 patient intolerable neurologic side effects at very low doses precluded mexiletine administration, while in 7 other patients noncardiovascular adverse effects were also noted.

Of 4 patients who received long-term oral mexiletine therapy, 3 had recurrence of VT (including 1 patient who had a successful response to mexiletine during serial electrophysiologic study) within a short period (1 to 16 weeks), while 1 patient has remained free of recurrence in 6 months of follow-up.

Comparison with previous serial electrophysiologic studies: The difference in results in the present study and the 2 previous studies from Ruskin's laboratory cannot be explained by differences in pacing technique or the amount of mexiletine used, since these were similar. The explanation may be related to a difference in the selection of study patients. Patients without inducible ventricular arrhythmia or patients with only nonsustained VT during the control electrophysiologic study were not included in our study. In the study of Di Marco et al.,[14] only 22 of 41 patients had inducible sustained VT during initial electrophysiologic study. Of these 22 patients, mexiletine was effective in 4 as a single agent, and in 2 as part of a combination regimen. This represents a total response rate of 27%, and an 18% response rate when mexiletine was used as a single agent. While these rates are lower than the reported success rate of 42% when all 41 patients with various ventricular arrhythmias are considered, they are still somewhat higher than the success rate of 9% (1 of

17) in our study. Further comparison of the study population regarding the extent and severity of the heart disease, which may have some influence on drug responsiveness, is not possible since these data were not reported in their study.

In the study of Ruskin et al.,[13] only 11 of 31 patients had inducible sustained VT and 2 of 31 had inducible ventricular fibrillation during the initial electrophysiologic study. Further comparison with the present series is not possible, since the necessary data were not reported in detail. Other possible sources of differences could be the varying end points considered as successful response in the different studies and the use of mexiletine in combination with other drugs. We did not use mexiletine as part of combination regimen in the present study. Di Marco et al.[14] also made the observation that mexiletine seemed more effective in suppressing rapid (cycle length less than 325 ms) rather than slower inducible arrhythmias. We did not observe this in the present study.

Adverse effects: We observed significant neurologic or gastrointestinal side effects, most requiring dose reduction or discontinuation in 8 of 17 patients (47%). This incidence of side effects is similar to recently reported findings.[12,14–16] However, the occurrence of serious and life-threatening arrhythmia potentiation in 5 of 17 patients (29%) represents an unexpectedly high incidence of this adverse effect. This frequency is higher than that reported by Heger et al.[15] (2 of 15, or 13%) or Di Marco et al.[14] (5 of 41, or 12%).

Clinical implications: Our observations indicate that oral mexiletine is ineffective in the therapy of patients with drug-refractory, recurrent sustained VT as defined by serial electrophysiologic studies and limited clinical follow-up. In addition, its use is associated with a high incidence of adverse effects, which in a significant proportion of patients can be serious and life-threatening. Therefore, oral mexiletine does not appear useful in the therapy of drug-refractory, paroxysmal sustained ventricular VT and, if used, it should be with caution and with an awareness of its potential for serious arrhythmia potentiation.

Acknowledgment

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Prolongation of the Human Cardiac Monophasic Action Potential by Sotalol

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Sotalol and propranolol are nonselective beta-adrenergic blocking agents. Sotalol at low concentration, unlike propranolol, prolongs the duration of the transmembrane action potential. In a double-blind study, the electrophysiologic effects of intravenous sotalol (0.30 or 0.60 mg/kg; n = 9) were compared with intravenous propranolol (0.15 or 0.20 mg/kg; n = 8) in 17 patients with use of bipolar suction electrodes in the right atrium and right ventricle to determine whether sotalol prolongs the monophasic action potential duration in man. After administration of sotalol, there were significant increases (paired *t* test) in the Q-T interval ($p < 0.001$), right atrial effective refractory period ($p < 0.05$), right ventricular effective refractory period ($p < 0.005$), right atrial monophasic action potential duration at 90% repolarization ($p < 0.01$), and right ventricular monophasic action potential duration at 90% repolarization ($p < 0.005$). Prolongation of the monophasic action potential duration was dependent on plasma sotalol concentration. There were no significant changes in these variables after propranolol. The spontaneous cycle length and Wenckebach cycle length increased significantly in both groups, and the mean blood pressure decreased in both, although not significantly after propranolol.

In summary, sotalol but not propranolol prolonged atrial and ventricular effective refractory periods and lengthened the monophasic action potential and the Q-T interval of human myocardium after intravenous infusion. The ability to acutely prolong repolarization at therapeutic plasma concentration is unique among known competitive beta-adrenergic receptor antagonists.

Sotalol is a nonselective beta-adrenergic receptor antagonist without intrinsic sympathomimetic or membrane-stabilizing activity. It has one third the beta-blocking potency of propranolol.[1] Earlier in vitro investigation of canine, feline, and rabbit preparations demonstrated prolongation of transmembrane action potentials in atrial and ventricular tissue during sotalol superfusion.[2,3] Monophasic action potentials can be measured in man utilizing a suction electrode catheter.[4] Duration of the monophasic action potential correlates well with the duration of the cellular action potential obtained with microelectrodes. Recently, Edvardsson[5] reported that intravenous sotalol significantly increased the right ventricular effective refractory period and monophasic action potential duration in 8 patients with chronic atrial fibrillation.

The purpose of this study was to explore the effects of sotalol on the electrophysiologic function of the heart in catheterized patients, to determine the degree of change in those effects with differing doses of sotalol, and to compare the changes with those produced by equipotent beta-blocking doses of propranolol.

Methods

Study subjects: Patients undergoing routine cardiac catheterization for clinical indications consented to electrophysiologic testing after angiography. Patients with New York Heart Association[6] functional class IV congestive heart failure, other contraindications to beta-blocking agents, major conduction disturbance in the electrocardiogram, or relative contraindication to withdrawal of ongoing beta-blocking therapy were excluded from participation in this study. All

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antiarrhythmic agents except digoxin were discontinued at least 24 hours before the study. Patients were studied in the postabsorptive state and were unsedated except for premedication with diazepam, 10 mg orally. The patients were assigned by double-blind randomization to receive sotalol hydrochloride (MJ 1999, Mead Johnson Pharmaceutical, Evansville, Indiana), 0.30 or 0.60 mg/kg body weight, or propranolol hydrochloride, 0.15 or 0.20 mg/kg, delivered intravenously over 15 minutes by way of a constant infusion pump. The propranolol dose was increased after the study had begun, based on further data regarding relative beta-blocking potency of the 2 drugs. The sotalol dose was reduced to 0.30 mg/kg after the 10th study patient.

Electrophysiologic study: Quadripolar pacing catheters were positioned in the high right atrial region and the right ventricular apex. As described in detail by Olsson et al.[7] and Samuelsson and Sjöstrand,[8] a saline-filled suction electrode catheter (MAP Catheter, Kifa AB, Sweden) was advanced into the right atrial or ventricular cavity until the tip made contact with the endocardium. A 3-way stopcock allowed selection of either infusion of saline solution or negative pressure of 200 to 300 mm Hg from a wall suction. Application of suction enabled bipolar recording of amplified direct current signals from the central and peripheral catheter electrode terminals. Surface electrocardiographic leads I, aVF, and V_1 were recorded simultaneously with the right atrial and right ventricular electrograms and monophasic action potential tracing. An indwelling right femoral arterial catheter provided continuous systemic pressure monitoring.

Stimulation testing was performed with 2 ms square wave pulses of amplitude twice diastolic capture threshold by means of a programmable stimulator (W.P. Instruments, New Haven, Connecticut). Mean arterial blood pressure, basic intervals, Wenckebach cycle length, right atrial and right ventricular effective refractory periods, and right atrial and right ventricular monophasic action potential durations were determined in both spontaneous and constant-paced rhythms before and after infusion of either sotalol or propranolol. The same pacing cycle length was used before and after administration. The QRS and Q-T intervals were measured from the limb leads during atrial-paced rhythm and expressed as the average of 5 consecutive cycles. The Wenckebach cycle length was determined during constant atrial pacing by decreasing the cycle length 10 ms every 10 seconds, and defined as the longest atrial cycle length resulting in atrioventricular nodal Wenckebach periodicity. The right atrial and right ventricular effective refractory periods were determined in constant atrial and ventricular paced rhythms, respectively, with premature extrastimuli introduced after every 8 paced basic drive beats. The longest coupling interval of the premature extrastimulus not resulting in atrial or ventricular depolarization was the effective refractory period of that chamber. Measurements of right atrial and right ventricular action potential durations were averaged over 3 consecutive beats and determined at 50, 90, and 100% repolarization. Samples for plasma drug levels were collected from the arterial catheter before drug infusion (time 0) and at 15, 30, and 45 minutes. Drug concentrations were determined with high performance liquid chromatography.

Statistical methods: The changes in spontaneous heart rate, Q-T interval, Wenckebach cycle length, right atrial and right ventricular effective refractory periods, and right atrial and right ventricular monophasic action potential durations at 90% repolarization in constant paced rhythm were compared before and after drug administration using a two-tailed paired *t* test. Changes in right atrial and right ventricular monophasic action potential durations at 90% repolarization and right atrial and right ventricular effective refractory periods determined at different drug doses were compared with two-tailed mean *t* tests. Plasma drug levels were attained and changes in monophasic action potential durations and effective refractory periods were analyzed using Spearman's rank correlation coefficient and Fisher's method for combining independent probabilities. When appropriate, standard deviations are provided.

Results

Seventeen men were studied. Nine received sotalol and 8 received propranolol. The mean age was 53 ± 13 years in the sotalol group and 54 ± 10 years in the propranolol group. The indication for cardiac catheterization was coronary heart disease in 8 patients in the sotalol group and 6 in the propranolol group. One patient had atrial arrhythmia in the sotalol group, and 1 patient each had mitral valve prolapse and atrial septal defect in the propranolol group. The New York Heart Association functional class for symptions of congestive heart failure was determined to be class I in 8 sotalol and 6 propranolol patients, class II in 2 propranolol patients, and class III in 1 sotalol patient. Four patients received sotalol, 0.30 mg/kg, and 5 received 0.60 mg/kg. Two patients received propranolol, 0.15 mg/kg, and 8 received 0.20 mg/kg.

Electrophysiologic findings: The basic rhythm was sinus in all 17 patients except 1 with atrial fibrillation in the sotalol group in whom data requiring right atrial pacing could not be obtained. In all patients in both sotalol and propranolol groups the spontaneous cycle length and Wenckebach cycle length increased after drug infusion (Table I). Mean arterial pressure decreased from 101 to 89 mm Hg ($p < 0.005$) in the sotalol group and from 102 to 97 mm Hg in the propranolol group (difference not significant [NS]). The Q-T interval ($p < 0.001$), right atrial effective refractory period ($p < 0.05$), right ventricular effective refractory period ($p < 0.05$), right atrial monophasic action potential at 90% repolarization ($p < 0.01$), and right ventricular monophasic action potential at 90% repolarization ($p < 0.005$) increased in all patients receiving sotalol, but did not increase in any patient receiving propranolol. Right atrial and right ventricular monophasic action potential durations at 50 and 100% repolarization were prolonged to the same extent as at 90% repolarization after sotalol.

An example of prolongation of the right ventricular monophasic action potential by sotalol is shown in Figure 1. Figure 2, recorded from a patient who received propranolol, demonstrates no change in right atrial monophasic action potential duration at 90% repolarization. The mean increases in right atrial and right ventricular monophasic action potentials and right atrial and right ventricular effective refractory periods were slightly, but not significantly, greater in patients receiving 0.60 mg/kg than in those receiving 0.30 mg/kg of sotalol. There were no changes in these variables after administration of either dose of propranolol.

Drug levels: The mean peak plasma sotalol level obtained at the end of drug infusion was 2.61 ± 0.67

TABLE I Drug-Related Changes in Electrophysiologic Variables

	Sotalol							Propranolol						
	Mean Before	Mean After	Change ± SD	Increased (n)	Decreased (n)	Unchanged (n)	p	Mean Before	Mean After	Change ± SD	Increased (n)	Decreased (n)	Unchanged (n)	p
BCL (ms)	923	1052	+129 ±44	9	0	0	0.001	817	963	+146 ±98	8	0	0	0.005
Q-T (ms)	381	419	+38 ±16	9	0	0	0.001	385	382	−3.0 ±20	3	1	4	NS
WCL (ms)	358	435	+77 ±51	6	0	0	0.02	357	417	+60 ±41	7	0	0	0.01
MBP (mm Hg)	101	89	−12 ±7.8	0	7	2	0.005	102	97	−5.0 ±6.5	0	2	6	0.1
RA MAPD 90% (ms)	263	307	+44 ±20	6	0	0	0.01	251	250	−1.0 ±5.6	0	1	5	NS
RV MAPD 90% (ms)	313	344	+31 ±9.4	5	0	0	0.005	276	273	−3.0 ±17	1	1	3	NS
RA-ERP (ms)	235	289	+54 ±48	6	0	0	0.05	246	253	+7.0 ±23	3	2	3	NS
RV-ERP (ms)	252	277	+25 ±10	6	0	0	0.005	259	260	+1.0 ±19	2	2	3	NS

* Two-tailed paired *t* tests were utilized. Number increased or decreased refers to the number of patients in whom the variable changed by 10 ms or more. Number unchanged refers to the number of patients in whom the variable changed by less than 10 ms. Q-T intervals were measured during constant paced rhythm. BCL = basic cycle length; RA-ERP = right atrial effective refractory period; MBP = mean blood pressure; RA-MAPD 90% = monophasic action potential duration measured at 90% repolarization from the right atrial endocardium; RV-ERP = right ventricular effective refractory period; RV-MAPD 90% = monophasic action potential duration measured at 90% repolarization from the right ventricular endocardium; WCL = Wenckebach cycle length.

FIGURE 1. Right ventricular monophasic action potential duration (RV-MAPD) at 90% repolarization before and after administration of sotalol, 0.60 mg/kg, during right ventricular paced rhythm.

FIGURE 2. Right atrial monophasic action potential duration (RA-MAP) at 90% repolarization before and after propranolol, 0.20 mg/kg, during right atrial paced rhythm.

μg/ml in patients receiving doses of 0.60 mg/kg and 1.58 ± 0.33 μg/ml in those receiving 0.30 mg/kg. At the conclusion of propranolol infusions the mean peak plasma level was 370 ± 160 ng/ml after doses of 0.20 mg/kg and 200 ± 80 ng/ml after 0.15 mg/kg. There was no statistical correlation between the changes in effective refractory periods or monophasic action potential durations and peak plasma sotalol levels. Sotalol plasma levels obtained 15 minutes after infusion (when most electrophysiologic measurements were recorded) were correlated with the extent of prolongation of the monophasic action potential duration ($p < 0.05$, 2-tailed) with use of the combined probabilities of the right atrial and right ventricular monophasic action potential durations calculated by Fisher's method.

Discussion

Sotalol versus propranolol: This study demonstrates that intravenous sotalol in man prolongs the monophasic action potential durations and effective refractory periods of both atrial and ventricular myocardium whereas intravenous propranolol, in equipotent beta-blocking doses,[1,9] does not. Although the monophasic action potential duration is obtained from only a small volume of myocardial tissue, the increase in effective refractory periods and Q-T intervals suggest a generalized effect. The increase in monophasic action potential duration provides evidence for a class III cellular effect of sotalol, which has not been reported for other beta-blocking agents after intravenous administration. Contrary to the previous prediction, based on microelectrode studies, that large concentrations of sotalol would be necessary for action potential prolongation,[10] these effects are present with clinically used dosages. With intravenous administration, the prolongation in monophasic action potential duration was not significantly related to either sotalol dose or peak plasma level. However, monophasic action potential tracings were recorded approximately 15 minutes after the peak plasma levels were attained, at which time the prolongation of the monophasic action potential duration was directly correlated with plasma concentration.

Comparison with previous studies: Our findings are in agreement with those of previous animal investigations. Prolongation of the transmembrane action potential by sotalol has been described in canine Purkinje tissue and ventricular muscle, rabbit atrial tissue, and cat papillary muscle.[2,3] In vitro animal studies with propranolol by Davis et al.[11] showed a decrease in transmembrane action potential duration and effective refractory period in canine Purkinje fibers, but only at large concentrations (3 μg/ml and greater). This shortening effect was recently demonstrated in human subjects with use of the suction electrode technique.[12] In our study, the mean peak plasma propranolol level obtained for doses of 2 mg/kg was 0.37 μg/ml, and fell to less than 0.10 μg/ml during electrophysiologic measurements. Therefore, our findings of no change in monophasic action potential duration after propranolol are consistent with previous experimental results.[11,12] Recent human studies with sotalol have been contradictory. Ward et al.[13] found an increase in the atrial effective refractory period but not in the ventricular effective refractory period. Edvardsson[5] found an increase in both the right ventricular effective refractory period and right ventricular monophasic action potential duration after sotalol, but did not measure the atrial effective refractory period. He found that the sinus nodal recovery times and atrio-His bundle conduction times were prolonged after intravenous sotalol, as occurs after propranolol.

Methodology: The monophasic action potential determined with suction electrode is not a true representation of the transmembrane action potential, but rather a reflection of injury effects. However, Shabetai et al.[4] compared monophasic action potential recordings in man with transmembrane action potential recordings in animals, and found the potentials to have the same shape and duration, and similar responses to changes in heart rate, administration of calcium and digitalis, and to the introduction of premature extrasystoles. The monophasic action potential duration appears to be a quantitatively accurate index of the true action potential duration. The monophasic action potential recordings comprise a summation of a number of cells, have a lower amplitude, and cannot be equated with absolute transmembrane potential differences. Therefore, one cannot evaluate changes in action potential amplitude, resting membrane potential, or upstroke velocity using the suction electrode technique. Microelectrode studies have demonstrated no significant change in this variable after superfusion of sotalol or propranolol.[2]

Mechanism of action: Beta-adrenergic receptor antagonists inhibit the transmembrane action potential effects of catecholamines. In the absence of catecholamines, beta blockade generally does not alter the transmembrane action potential. Propranolol, but not sotalol, has been found to have weak direct membrane effects in addition to its beta-blocking properties. These class I effects include reduction in the action potential amplitude, upstroke velocity, membrane responsiveness, and conduction, and are probably due to decreased sodium influx.[10] Microelectrode studies demonstrate prolongation by sotalol of phases 2 and 3 of the action potential. Possible underlying mechanisms include augmentation of the slow inward current or a delay in onset or reduction of potassium efflux. At present there is no direct evidence to substantiate either mechanism.

There is some evidence that beta-blocking agents have different effects when administered acutely or chronically. After long-term administration of practolol in rabbits,[14] in vitro studies showed an increase in the atrial action potential duration. Long-term administration of metoprolol in human subjects was found to prolong the monophasic action potential duration, right ventricular effective refractory period, and Q-T interval.[5] Other evidence of Q-T prolongation exists for

propranolol and acebutolol.[5] It is possible that prolongation of the action potential duration is another property common to beta-blocking agents manifested acutely with sotalol, but requiring long-term therapy with other drugs.

Clinical implications: The unique combination in sotalol of class II and III actions could be beneficial in the management of arrhythmias. Amiodarone, a class III agent, has proved efficacious in the treatment of virtually all types of atrial and ventricular ectopic beats and tachyarrhythmias. Olsson et al.[15] found that long-term oral therapy with a small dose (200 mg daily) of amiodarone increased the right atrial monophasic action potential duration in 8 patients from an average of 234 to 308 ms. Although this prolongation was more pronounced than we observed with sotalol, Olsson et al. studied their patients with sinus rhythm, which was slowed by amiodarone. Intravenous and oral sotalol have been used in the treatment of atrial and ventricular arrhythmias with moderate effectiveness.[16–18] However, the studies included patients with heterogeneous arrhythmia with differing doses and routes of administration, making comparative assessment difficult. We evaluated only the intravenous effects of sotalol. Oral sotalol should be studied with cellular action potential recordings to assess whether prolongation of the action potential persists. Significant prolongation of the Q-T interval has already been reported, providing indirect evidence.

At present, clinical trials are being carried out in patients who have had a myocardial infarction to determine whether sotalol is effective in the prevention of sudden cardiac death. It is possible that the combination of beta-adrenergic receptor blockade and class III action produced by sotalol would offer greater benefit than beta blockade alone.

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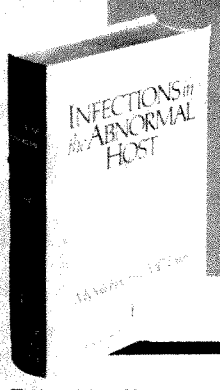

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SEVERAL PREPARATIONS OF NITROGLYCERIN FOR INJECTION ARE AVAILABLE. THEY DIFFER IN CONCENTRATION AND/OR VOLUME PER VIAL. WHEN SWITCHING FROM ONE PRODUCT TO ANOTHER ATTENTION MUST BE PAID TO THE DILUTION AND DOSAGE AND ADMINISTRATION INSTRUCTIONS.

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TRIDIL should not be administered to individuals with:

1. A known hypersensitivity to nitroglycerin or a known idiosyncratic reaction to organic nitrates.
2. Hypotension or uncorrected hypovolemia, as the use of TRIDIL in such states could produce severe hypotension or shock.
3. Increased intracranial pressure (e.g., head trauma or cerebral hemorrhage).
4. Constrictive pericarditis and pericardial tamponade.

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1. Nitroglycerin readily migrates into many plastics. To avoid absorption of nitroglycerin into plastic parenteral solution containers, the dilution and storage of TRIDIL for intravenous infusion should be made only in *glass* parenteral solution bottles.
2. Some filters absorb nitroglycerin; they should be avoided.
3. Forty to 80% of the total amount of nitroglycerin in the final diluted solution for infusion is absorbed by the polyvinylchloride (PVC) tubing of the intravenous administration sets currently in general use. The higher rates of absorption occur when flow rates are low, nitroglycerin concentrations are high, and the administration set is long. Although the rate of loss is highest during the early phase of infusion (when flow rates are lowest) the loss is neither constant nor self-limiting; consequently no simple calculation or correction can be performed to convert the theoretical infusion rate (based on the concentration of the infusion solution) to the actual delivery rate.

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Excessive hypotension, especially for prolonged periods of time, must be avoided because of possible deleterious effects on the brain, heart, liver, and kidney from poor perfusion and the attendant risk of ischemia, thrombosis, and altered function of these organs. Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Patients with normal or low pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of TRIDIL. If pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension, and the pulmonary capillary wedge pressure is thus a useful guide to safe titration of the drug.

Carcinogenesis, mutagenesis, impairment of fertility

No long-term studies in animals were performed to evaluate carcinogenic potential of TRIDIL.

Pregnancy

Category C. Animal reproduction studies have not been conducted with TRIDIL. It is also not known whether TRIDIL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TRIDIL should be given to a pregnant woman only if clearly needed.

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It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRIDIL is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of TRIDIL in children have not been established.

ADVERSE REACTIONS

The most frequent adverse reaction in patients treated with TRIDIL is headache, which occurs in approximately 2% of patients. Other adverse reactions occurring in less than 1% of patients are the following: tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain.

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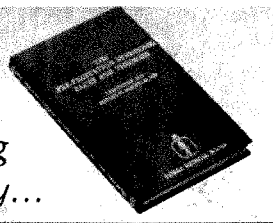

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC

Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC

Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

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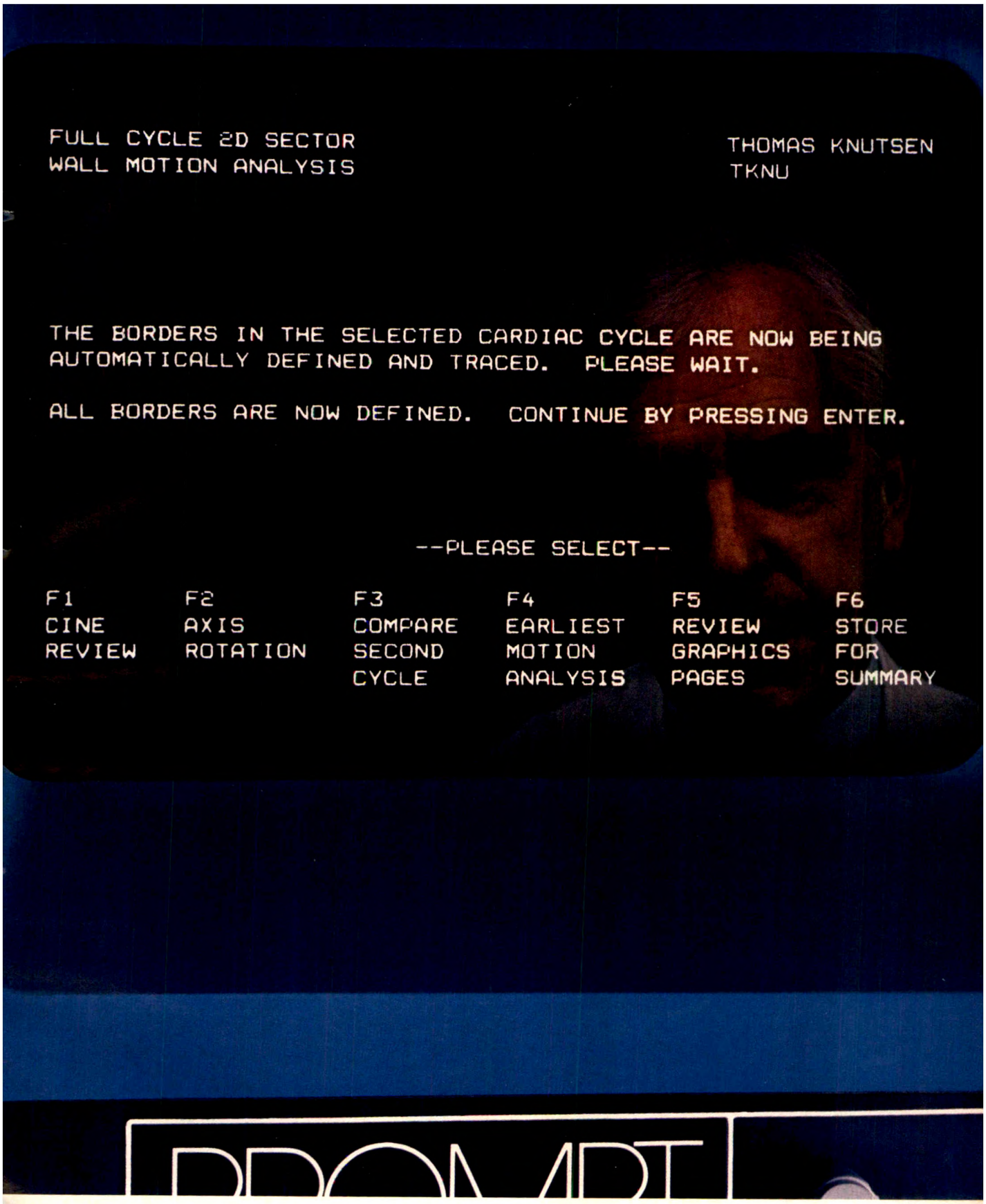

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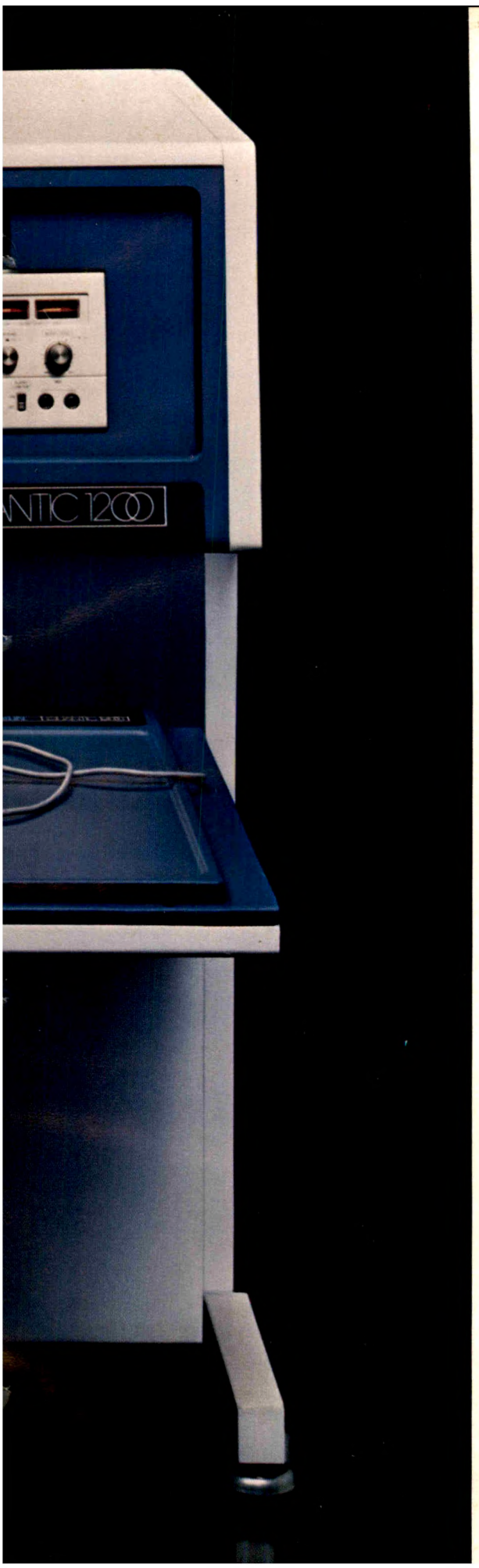

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Use of Procainamide in Patients With the Wolff-Parkinson-White Syndrome to Disclose a Short Refractory Period of the Accessory Pathway

HEIN J. J. WELLENS, MD, SIMON BRAAT, MD, PEDRO BRUGADA, MD, ANTON P. M. GORGELS, MD, and FRITS W. BÄR, MD

Like ajmaline, procainamide can be used to identify patients with the Wolff-Parkinson-White syndrome who have a short refractory period of the accessory pathway in an anterograde direction. Procainamide given intravenously in a maximal dose of 10 mg/kg body weight over a 5 minute period during sinus rhythm produced complete anterograde block in the accessory pathway in 20 of 39 patients. An electrophysiologic investigation performed 24 to 48 hours later revealed that in 19 of the 20 patients the effective refractory period of the accessory pathway was 270 ms or greater. In 18 of the 19 patients not exhibiting anterograde block in the accessory pathway, the refractory period was less than 270 ms. When ajmaline was compared with procainamide in the same patient, 100 mg of procainamide had approximately the same effect as 10 mg of ajmaline. The use of intravenous procainamide is a reliable and rapid method of identifying patients with the Wolff-Parkinson-White syndrome who may be at risk for circulatory insufficiency or sudden death in case of atrial fibrillation.

In patients with the Wolff-Parkinson-White syndrome a correlation exists between the duration of the refractory period of the accessory pathway in an anterograde direction and the shortest R-R interval between preexcited QRS complexes during atrial fibrillation.[1–3] Deterioration of atrial fibrillation into ventricular fibrillation has been reported in patients with short refractory periods of their accessory pathway in an anterograde direction.[4] We previously reported on the use of ajmaline to identify patients with the Wolff-Parkinson-White syndrome having an anterograde refractory period of the accessory pathway of 270 ms or less.[5] Because ajmaline is not available in the United States we became interested in studying the potential value of intravenous procainamide to obtain the same information.

Methods

Patients: Thirty-nine patients with electrocardiographic characteristics of the Wolff-Parkinson-White syndrome were studied. Their ages ranged from 7 to 65 years; 27 patients were male and 12 female. Twenty-seven patients had electrocardiographic documentation of a regular supraventricular tachycardia. In 7 patients atrial fibrillation had been recorded. In 3 patients electrocardiograms showing both atrial fibrillation and a regular supraventricular tachycardia were available. Two patients had no symptoms. During programmed stimulation of the heart the accessory atrioventricular pathway was located between the left atrium and the left ventricle in 19 patients, between the right atrium and the right ventricle in 8 patients, and in the septum in 12.

Protocol: The following protocol was used in all patients:

1. An echocardiogram was made to exclude the presence of idiopathic hypertropic subaortic stenosis.[6]
2. All medication was withheld for at least 4 days.
3. (a) Twenty-four to 48 hours before a programmed stimulation study and after a 12 lead electrocardiogram revealed sinus rhythm with the Wolff-Parkinson-White pattern, a maximal dose of 50 mg of ajmaline was given intravenously over a 3 minute period. Six electrocardiographic leads (I, II, III, V_1, V_5, and V_6) were simultaneously and continuously recorded during the registration. If no block in the accessory atrioventricular pathway occurred the recording was stopped 15 minutes after the end of the injection. (b) Six hours after administration of ajmaline, procainamide was given intravenously during sinus rhythm in a maximal dose of 10 mg/kg body weight over a 5 minute period. During the injection the same electrocardiographic leads were continuously and simultaneously recorded as during the injection of ajmaline. If no block in the accessory atrioventricular pathway occurred, the recording was stopped 20 minutes after the end of the procainamide injection.
4. Twenty-four to 48 hours later after informed consent was obtained, a programmed electrical stimulation study was performed[7] and the duration of the anterograde refractory period of the accessory pathway was measured using the single test stimulus technique during atrial pacing. At least 3 different basic cycle lengths were used. The effective anterograde refractory period of the accessory pathway was defined as the shortest atrial premature stimulus interval showing atrioventricular conduction over the accessory pathway from the

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TABLE I **Data on the Effective Refractory Period of the Accessory Pathway (ERPAP) in an Anterograde Direction and the Dose of Ajmaline and Procainamide to Produce Anterograde Block in the Accessory Pathway (AP)**

Case	Age (yr) & Sex	ERPAP	Anterograde Block in AP	Ajmaline (mg)	Procainamide (mg)
1	40F	270	+	35	400
2	19M	260	+	45	450
3	34F	270	+	35	400
4	49M	270	+	30	300
5	32M	400	+	30	300
6	34M	270	+	40	375
7	36M	600	+	35	400
8	16M	500	+	10	100
9	33M	330	+	30	300
10	65F	300	+	50	400
11	23M	280	+	35	350
12	18F	300	+	40	450
13	41F	290	+	35	350
14	21M	380	+	50	350
15	31M	410	+	20	250
16	27M	290	+	40	400
17	29M	280	+	40	450
18	40M	320	+	50	500
19	11F	270	+	50	500
20	21M	300	+	50	375
21	28F	<230	−	50	700
22	48M	<260	−	50	800
23	35M	180	−	50	750
24	41F	230	−	50	600
25	20M	230	−	50	650
26	37M	290	−	50	800
27	16M	290	−	50	600
28	45M	240	−	50	850
29	26M	<230	−	50	750
30	7F	210	−	50	350
31	40M	200	−	50	850
32	29M	240	−	50	750
33	21F	<200	−	50	650
34	23M	230	−	50	700
35	36M	<190	−	50	850
36	18M	200	−	50	700
37	48F	210	−	50	850
38	22F	<210	−	50	600
39	23M	240	−	50	680

+ = present; − = absent.

atrial stimulation site closest to the atrial end of the accessory pathway. In all patients in whom administration of ajmaline, procainamide, or both resulted in anterograde block in the accessory pathway, the respective dosages of ajmaline and procainamide were compared.

Results

Relation between effects of ajmaline and procainamide and duration of the effective refractory period of the accessory pathway: In 20 patients anterograde conduction over the accessory pathway could be blocked by administration of both ajmaline and procainamide. Data on the doses required and the duration of the effective refractory period of the accessory pathway in an anterograde direction are given in Table I. A typical example of anterograde block in the accessory pathway after procainamide administration is shown in Figure 1. All but 1 of the 20 patients who had anterograde block in the accessory pathway had a duration of the effective refractory period of the accessory pathway in the anterograde direction of 270 ms or more.

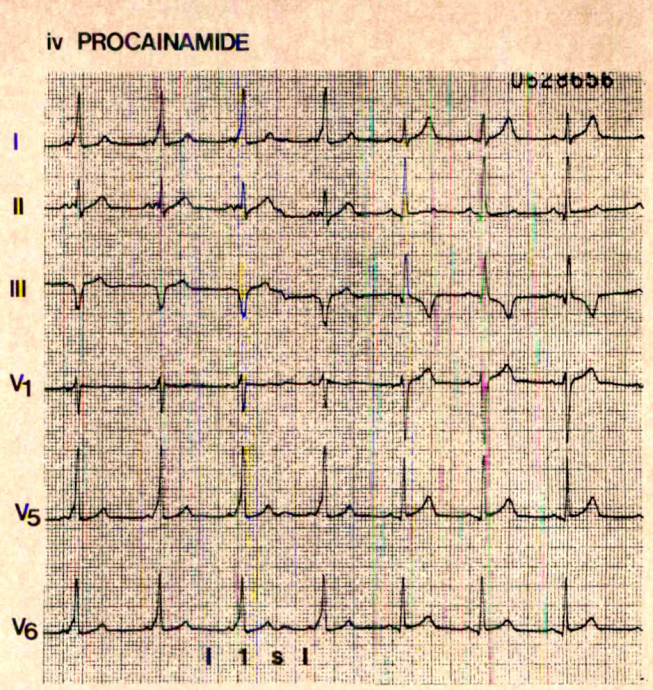

FIGURE 1. Example of the creation of complete anterograde block in the accessory pathway by injection of 300 mg of procainamide intravenously. Leads I, II, III, V_1, V_5, and V_6 were recorded simultaneously. Note the disappearance of preexcitation in the middle of the figure.

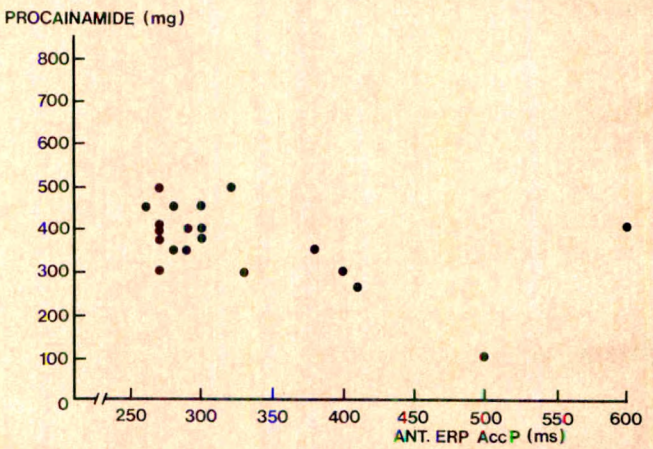

FIGURE 2. Amount of procainamide required to produce complete anterograde block in the accessory pathway (AccP) in relation to the predrug value of the anterograde (ANT.) refractory period (ERP) of the accessory pathway.

TABLE II **Relation Between Effect of Ajmaline and Procainamide on Anterograde Conduction Over the Accessory Pathway (AP)**

	Ajmaline	
Procainamide	Block AP Present	Block AP Absent
Block AP present	20	0
Block AP absent	0	19

In 18 of 19 patients not exhibiting anterograde block in the accessory pathway after administration of the drugs, the duration was 260 ms or less. Table II shows the excellent correlation between the effect of procainamide, and ajmaline and the production of complete anterograde block in the accessory pathway. Figure 2 shows that usually less procainamide was required to produce complete anterograde block in the accessory pathway the longer the predrug value of the duration of the anterograde refractory period of the accessory pathway.

Comparison of the dosages of ajmaline and procainamide required to produce anterograde block in the accessory pathway: Patients not needing the maximal dose of ajmaline (50 mg) to produce anterograde block in the accessory pathway never required the full dose of procainamide (10 mg/kg body weight) (Table I). However, in 2 patients a dose of less than the maximal dose of procainamide produced anterograde block whereas 50 mg of ajmaline was required to achieve the same result. Table I suggests that approximately 10 mg of ajmaline is equivalent to 100 mg of procainamide.

Side effects: Six patients complained of a warm feeling in the face during ajmaline injection. In 3 a visible flush developed. Three patients had dizziness during and for 3 to 10 minutes after the administration of procainamide.

Discussion

In 1964 Puech et al.[8] reported on the similar effects of procainamide and ajmaline in patients with the Wolff-Parkinson-White syndrome. This was confirmed by subsequent electrophysiologic studies.[9–12] Observation of the relation between the effects of ajmaline, quinidine, procainamide and amiodarone on the duration of the anterograde refractory period of the accessory pathway and the initial value for the duration of the anterograde refractory period of the accessory pathway[10] prompted us to compare the value of ajmaline and procainamide to identify patients with the Wolff-Parkinson-White syndrome having a short anterograde refractory period of the accessory pathway. Our results indicate that failure to produce anterograde block in the accessory pathway with procainamide given intravenously in a dose of 10 mg/kg over 5 minutes strongly suggests a short anterograde refractory period of the accessory pathway. The electrophysiologic effects of procainamide given in this way last approximately 1 hour.[9] Because of a possible hypotensive effect and the possibility of a delaying or blocking effect on subnodal conduction accompanying anterograde block in the accessory pathway, we believe that procainamide should be given under well-controlled hospital conditions.

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Electrophysiologic Effects of Flecainide Acetate in Patients With Sinus Nodal Dysfunction

HARALD VIK-MO, MD, OLE-JØRGEN OHM, MD, and PER LUND-JOHANSEN, MD

Flecainide acetate (R818) is a new antiarrhythmic agent for oral and intravenous use; it has predominantly class I properties and a long plasma half-life. Electrophysiologic effects were evaluated in 11 patients with sinus nodal dysfunction before administration of flecainide acetate and 15 to 60 minutes after intravenous administration of 1.5 mg/kg body weight of flecainide acetate given over 15 minutes. In 8 of 11 patients the maximal sinus nodal recovery time increased after flecainide acetate. However, the mean maximal sinus nodal recovery time was not statistically significantly increased from 1,929 ± 184 (mean ± standard error of the mean [SEM]) to 2,770 ± 500 ms ($p < 0.10$). The corrected sinus nodal recovery time increased from 875 ± 181 before to 1,727 ± 507 ms after administration of flecainide acetate ($p < 0.05$). The sinus cycle length and sinoatrial conduction time were not significantly changed. Flecainide acetate induced a marked prolongation of the H-V interval (from 41 ± 3 to 52 ± 4 ms [$p < 0.01$]) as well as a significant increase in the A-H interval, QRS duration, and QT_{100} interval. The effective and functional refractory periods of the atria increased by 12% ($p < 0.01$) and 11% ($p < 0.01$), respectively. The atrioventricular (AV) nodal functional refractory period increased significantly by 7% ($p < 0.01$), whereas the 9% prolongation of the effective refractory period was not statistically significant. No side effects were observed. It is concluded that flecainide acetate prolongs atrial and ventricular conduction and refractoriness, and thus appears to be a potent antiarrhythmic agent. However, the sinus nodal function is depressed, and thus caution is advised in the use of flecainide acetate in patients with sinus nodal dysfunction.

Flecainide acetate (R818) is a structurally new antiarrhythmic drug with a predominantly class I mode of action, which can be given in oral and intravenous preparations.[1-4] It has a relatively long half-life in plasma of about 20 hours in patients with heart disease.[5,7] A low incidence of side effects has been reported.[5,8] Flecainide acetate has been shown to be effective against a variety of experimentally induced arrhythmias in animals.[1,9,10] In clinical studies its antiarrhythmic efficacy has been demonstrated in the management of ventricular arrhythmia,[5,6,11] Wolff-Parkinson-White syndrome, and AV nodal reentrant tachycardia.[8,12] Electrophysiologic studies in man have demonstrated a pronounced effect on infranodal and ventricular conduction, with lesser effects on the sinus node and atrium.[8,12,13]

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Patients with sinus nodal dysfunction frequently have supraventricular tachyarrhythmia.[14,15] The electrophysiologic response to antiarrhythmic drugs in these patients may differ from that in patients with normal sinus nodal function. Thus, several drugs with a class I mode of action (lidocaine, disopyramide, and mexiletine) have been reported to precipitate or exacerbate an abnormal sinoatrial function in patients with sinus nodal dysfunction[16-19]; however, this effect could not be anticipated from studies in healthy persons.

The purpose of this study was to assess the electrophysiologic effects of flecainide acetate on impulse formation, conduction, and refractoriness in patients with sinus nodal dysfunction.

Methods

Patients: The study was carried out during routine electrophysiologic evaluation in 11 patients with symptomatic chronic sinus bradycardia who had complaints of syncope, dizziness, or easy fatigability. Table I summarizes the clinical data on the patients. Informed consent was obtained from all patients. Sinus nodal dysfunction was documented by a 12 lead electrocardiogram (ECG) in all patients and by 24 hour Holter monitoring in some patients. All patients had sinus rhythm during the study with no clinical or radiologic evidence

TABLE I Clinical Data on the 11 Patients Investigated

Case	Age (yr) & Sex	Diagnosis	Major Rhythm Disturbance
1	59M	Primary sinus nodal disease	Sinus arrest
2	77F	Primary sinus nodal disease	Sinus bradycardia
3	75M	Coronary heart disease	Sinus bradycardia
4	62F	Coronary heart disease	SA block, grade II
5	67F	Coronary heart disease	SA block, grade II
6	71M	Coronary heart disease	Sinus bradycardia
7	72M	Primary sinus nodal disease	Sinus bradycardia
8	72F	Aortic valve disease	Sinus arrest, LAH, RBBB
9	77M	Hypersensitive carotid sinus	Sinus arrest
10	44M	Primary sinus nodal disease	Sinus arrest
11	72F	Primary sinus nodal disease	Tachybradyarrhythmia

LAH = left anterior hemiblock; RBBB = right bundle branch block; SA = sinoatrial.

of cardiac failure. Two patients (Cases 2 and 8) had the last dose of digitoxin 24 hours before the study (serum concentrations 10 and 11 ng/ml, respectively). In all other patients digitalis preparations were discontinued 2 weeks and other antiarrhythmic drugs 1 week before the study.

Electrophysiologic procedure: The patients were studied in the morning after an overnight fast. No premedication was given. Three electrodes were introduced using the percutanous Seldinger technique from a femoral vein. A quadripolar electrode was positioned in the right ventricle to record His bundle activity. Two bipolar electrodes were positioned in the right atrium, 1 for atrial pacing and the other for recording atrial activity. His bundle, right atrial, and surface electrocardiograms (leads I and III) were recorded on an Elema-Schonander Mingograph at a paper speed of 100 mm/s.

Methods: Programmed stimulation was performed using a Medtronic pulse generator model 5325 with a 1.8 ms pulse duration and output 3 times the diastolic threshold. Sinus nodal recovery time and corrected sinus nodal recovery time were studied with atrial overdrive pacing at rates of 80 to 160 beats/min,[20] and measured from the last paced atrial beat to the next spontaneous atrial or AV junctional escape beat. Maximal sinus nodal recovery time was defined as the longest atrial pause after the sudden cessation of pacing at any tested heart rate. Sinoatrial conduction time was measured by the atrial extrastimulus technique on spontaneous rhythm.[21] The refractory periods of the atrium and AV node were measured with the programmed extrastimulus technique during atrial pacing at a constant cycle length of 750 ms.[22] Refractory periods were calculated using the following terms: S is the pacing stimulus, A is the right atrial electrogram, H is the His bundle potential, and V is the earliest recorded ventricular activity taken from either surface leads or intracardiac electrograms. S_1, A_1, H_1, and V_1 were deflections from the last driving stimulus at a constant heart rate. S_2, A_2, H_2, and V_2 were deflections from the premature atrial stimulus. The effective refractory period of the atrium was defined as the longest S_1-S_2 interval at which S_2 failed to produce atrial depolarization, and the functional refractory period of the atrium as the shortest recorded A_1-A_2 interval. The effective refractory period of the AV node was defined as the longest A_1-A_2 interval at which A_2 failed to produce H_2, and the functional refractory period of the AV node as the shortest H_1-H_2 interval recorded. The A-H interval, used to define AV nodal conduction time, was measured from the initial deflection of A to the start of H deflections in the His bundle electrocardiogram. The H-V interval, representing the His-Purkinje conduction time, was measured from the start of the H deflection in the His bundle electrocardiogram to the earliest sign of ventricular activity in either recorded lead. Sinus cycle length (mean, 10 heart cycles) and QRS duration were measured during sinus rhythm. The Q-T interval was measured after 1 minute of atrial pacing at a rate of 100 beats/min (Q-T_{100} interval) from standard lead I.

Flecainide acetate administration: The studies were carried out before administration of flecainide acetate and repeated 30 minutes after the start of drug administration. Flecainide acetate was given in a dose of 1.5 mg/kg body weight as a slow intravenous injection over 15 minutes. Care was taken that the measurements were always obtained in the same order before and after drug administration. Venous blood samples for analysis of plasma concentrations of the drug were taken immediately before and 30 and 60 minutes after start of drug administration. Plasma concentrations of flecainide acetate were measured with gas-liquid chromatography.[5,23]

Statistical analysis: The patients served as their own controls. Comparisons were performed between corresponding registrations before and after drug administration using the Wilcoxon nonparametric test for paired data (two-tailed)[24]; $p < 0.05$ was regarded statistically significant.

Results

The infusion of flecainide acetate was accomplished without any extracardiac side effects. A few patients had transient dizziness during the electrophysiologic testing, but no patient had clinical symptoms related to administration of flecainide acetate. The mean arterial blood pressure was 107 ± 3 (mean ± SEM) before and 110 ± 3 mm Hg after drug administration (not statistically significant [NS], n = 11). The blood levels of flecainide acetate were 230 ± 74 and 200 ± 63 ng/ml 30 and 60 minutes after initiation of drug infusion, respectively.

Sinus nodal function: Sinus cycle length was not significantly changed by the drug (Table II). Maximal sinus nodal recovery time increased in 8 of the 11 patients. In 3 of these patients the prolongation of maximal sinus nodal recovery time was marked, ranging from 1,990 to 3,700 ms (Fig. 1). The maximal corrected sinus nodal recovery time was significantly increased by flecainide acetate ($p < 0.05$, n = 11). Before drug administration 5 patients had a prolonged sinoatrial conduction time of more than 120 ms. The sinoatrial conduction time was not significantly changed by flecainide acetate (NS, n = 8), although in the patient with the greatest prolongation, the value increased from 300 to 712 ms after drug administration. Sinoatrial conduction time could not be calculated in 2 patients because of an unstable sinus cycle length.

Intracardiac conduction: Flecainide acetate caused a prolongation of the QRS duration by 11% ($p < 0.01$, n = 11) and of the Q-T_{100} interval by 5% ($p < 0.01$, n = 11) (Table III). The A-H interval increased in 10 of 11 patients, ranging from 5 to 45 ms, and was unchanged in

TABLE II Sinus Nodal Function Before and After Administration of Flecainide Acetate

Case	Sinus Cycle Length (ms)		Maximal SNRT (ms)		Maximal CSNRT (ms)		SACT (ms)	
	Before	After	Before	After	Before	After	Before	After
1	1,332	1,177	1,700	1,760	368	583	136	136
2	1,010	999	2,480	5,470	1,470	4,471	300	712
3	1,431	1,326	1,970	1,920	539	594	58	95
4	915	835	3,140	5,130	2,225	4,295	...	...
5	842	820	1,800	1,970	958	1,150	...	...
6	1,085	1,121	1,570	2,285	485	1,164	177	170
7	1,206	1,157	2,640	2,155	1,434	998	60	135
8	1,136	1,241	1,955	2,155	819	914	242	213
9	708	725	1,065	1,090	357	365	22	104
10	944	960	1,325	1,270	381	310	109	88
11	985	1,117	1,570	5,270	585	4,153	211	205
Mean	1,054	1,043	1,929	2,770	875	1,727	146	206
SEM	64	58	184	500	181	507	31	65
p	NS		NS		<0.05		NS	

CSNRT = corrected sinus nodal recovery time; SACT = sinoatrial conduction time; SNRT = sinus nodal recovery time.

TABLE III QRS Duration, Q-T Interval, and Intracardiac Conduction Intervals Before and After Administration of Flecainide Acetate

Case	QRS Interval (ms)		Q-T Interval (ms)		A-H Interval (ms)		H-V Interval (ms)	
	Before	After	Before	After	Before	After	Before	After
1	70	80	330	350	110	130	45	55
2	45	50	350	350	125	125	40	50
3	60	80	365	380	100	110	40	62
4	65	70	340	350	110	130	30	45
5	60	65	330	350	85	130	45	55
6	70	70	330	360	125	150	45	70
7	80	90	345	380	170	195	30	35
8	150	170	415	440	180	185	60	75
9	55	65	310	330	135	155	50	55
10	90	95	340	370	130	155	35	40
11	65	70	370	350	95	110	35	35
Mean	74	82	348	365	124	143	41	52
SEM	8	10	8	9	9	8	3	4
p	<0.01		<0.01		<0.01		<0.01	

TABLE IV Atrial and AV Nodal Refractory Periods Before and After Administration of Flecainide Acetate

Case	Atrial Refractory Periods (ms)				AV Nodal Refractory Periods (ms)			
	A-ERP		A-FRP		AV-ERP		AV-FRP	
	Before	After	Before	After	Before	After	Before	After
1	220	320	320	360	405	420	490	490
2	310	315	360	365	...	...	460	465
3	265	302	335	350	...	...	410	440
4	224	230	280	285	228	234	410	420
5	240	245	280	290	...	...	390	400
6	310	335	355	370	315	340	475	475
7	260	290	325	370	370	300	460	470
8	355	425	415	485	390	420	470	500
9	...	...	245	275	245	275	345	395
10	200	225	260	245	370	390	455	465
11	290	295	320	480	295	475	295	480
Mean	267	298	317	352	327	357	424	454
SEM	16	19	15	23	24	29	18	11
p	<0.01		<0.01		NS		<0.01	

A-ERP and A-FRP = effective and functional refractory periods of the atrium; AV-ERP and AV-FRP = effective and functional refractory periods of the atrioventricular node.

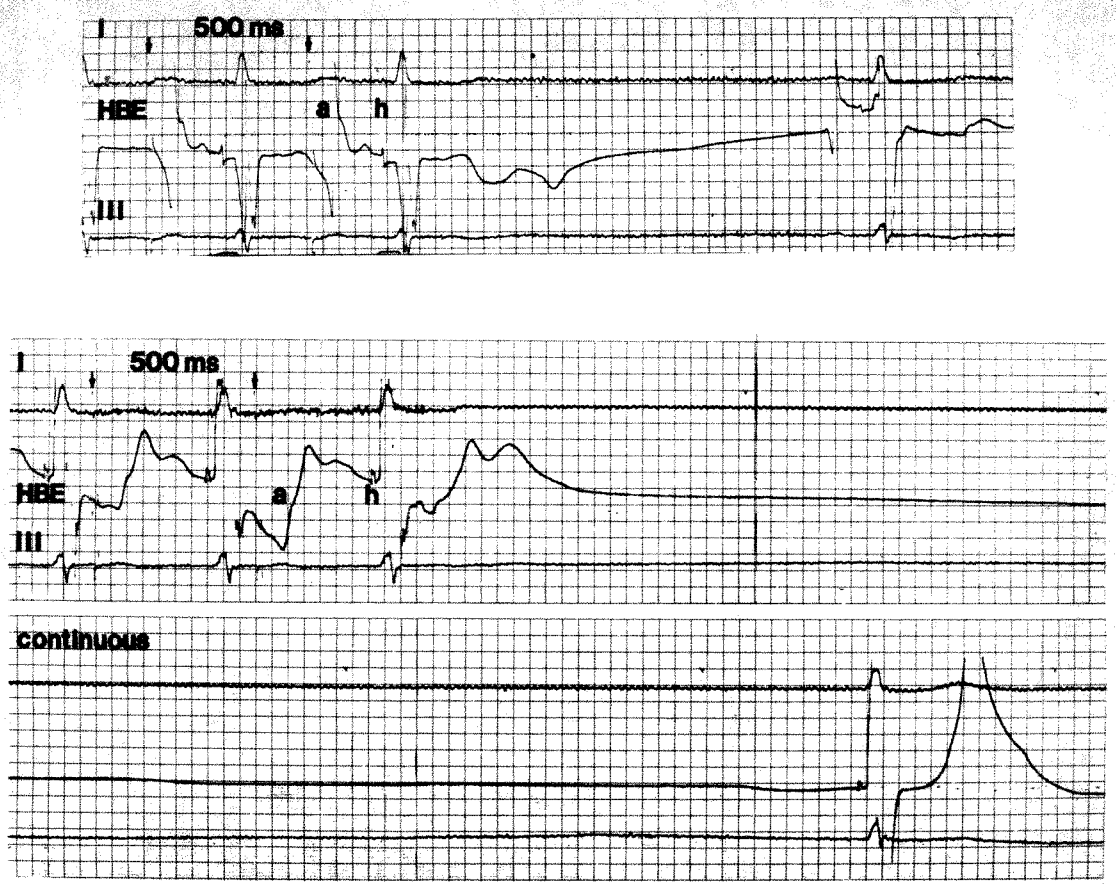

FIGURE 1. Representative electrocardiographic recordings from Patient 11. The longest sinus nodal recovery times recorded before (**upper strip**) and after flecainide acetate infusion (**lower strips, continuous**) are shown. After flecainide infusion sinus nodal recovery time was prolonged at all atrial pacing rates from 110 to 160 beats/min (2,760 to 5,270 ms). The longest pause shown occurred after an atrial pacing rate of 120 beats/min and was followed by an atrioventricular junctional escape beat. I and III = electrocardiographic standard leads I and III; a = atrial *a* wave; h = His deflection; HBE = His bundle ECG; ↓ = the 2 last pacing stimuli with a 500 ms interval.

1 patient ($p < 0.01$, n = 11). The pacing cycle length at which Wenckebach AV nodal block occurred was 140 ± 16 beats/min before and 135 ± 16 after drug administration, respectively (NS, n = 10). The H-V interval increased in 10 patients, ranging from 5 to 25 ms, and was unchanged in 1 patient ($p < 0.01$, n = 11). We did not observe H-V block in the patient with a prolonged H-V interval, left anterior hemiblock, and right bundle branch block (Case 8), or in the other patients with normal conduction.

Refractory periods: Both the effective and functional refractory periods of the atrium increased significantly after administration of flecainide, by 12% ($p < 0.01$, n = 11) and 11% ($p < 0.01$, n = 11), respectively (Table IV). The effective refractory period of the AV node could be measured in only 8 patients because the refractory period of the atrium was reached earlier in the 3 remaining patients. Flecainide acetate prolonged the AV nodal effective refractory period in 7 of the 8 patients (NS, n = 8). The A-V nodal functional refractory period increased in 9 patients and was unchanged in the other 2 ($p < 0.01$, n = 11).

Discussion

This study was designed to evaluate the electrophysiologic effects of flecainide acetate in patients with documented disturbances of sinus nodal function. The drug, 1.5 mg/kg body weight, given as a slow infusion over 15 minutes, had a mean plasma flecainide acetate level within the therapeutic range of the drug.[4,13] The drug was well tolerated and no side effects were observed.

The prolongation of sinus nodal recovery time found in our patients with sinus nodal dysfunction could not have been predicted from findings in animal experiments[1] or from studies in healthy persons,[25] in which essentially normal sinus nodal recovery time is reported after administration of flecainide acetate. However, Seipel et al.,[13] using flecainide acetate in doses of 1.0 and 2.0 mg/kg in patients with normal sinus nodal function, found a 37% prolongation of corrected sinus nodal recovery time at the larger dose, with no effect observed at the smaller dose. They suggested that a dose-related depression of the sinus nodal function by flecainide

acetate might be present. In our patients with documented sinus nodal dysfunction, a more pronounced prolongation (97%) of corrected sinus nodal recovery time was found. In 3 of 11 patients prolongation of the corrected sinus nodal recovery time was marked, ranging from 2,070 to 3,568 ms. The cause of the depressant effect of flecainide on sinus nodal function observed in this study is not known. Spontaneous variation in autonomic tone seems unlikely because basic cycle length was the same before and after drug infusion. Several drugs with class I properties are known to severely aggravate abnormal sinus nodal function, but the mechanism for this effect is not clear.[16,19] In addition to a possible direct membrane depressant effect on the sinus node caused by the drug, a more profound suppression of the sinus node during atrial overdrive pacing might occur. Drugs with a vagolytic effect have been shown to prolong sinus nodal recovery time because of facilitation of retrograde sinoatrial conduction and thereby allow more pronounced suppression of the sinus node during atrial overdrive pacing.[26] However, the sinoatrial conduction time, estimated by the extrastimulus technique used in this study, revealed no significant change after drug administration. It is therefore less likely that our observed depressant effect on sinus nodal function is due to enhancement of retrograde sinoatrial conduction during atrial pacing.

In accordance with earlier investigations, we found reduced AV nodal and intraventricular conduction times after administration of flecainide acetate.[8,13] The most profound effect was on intraventricular conduction, where we found an 11% increase in the QRS duration and a 27% increase in the H-V interval. This effect on infranodal conduction is more pronounced than in animal experiments,[1] but is similar to other studies in man.[8,24] None of our patients exhibited higher degrees of AV block. The only patient (Case 8) in this study who had an intraventricular conduction disturbance had an increase in AV and H-V intervals similiar to the other patients. However, Seipel et al.[13] described 2 patients with bundle branch block who had infranodal block after receiving a large dose of flecainide acetate (2 mg/kg) intravenously. Further clinical experience is necessary to define the importance of these findings in patients with AV conduction disturbances. However, the potency of the drug for depressing AV conduction is a beneficial property in the treatment of tachyarrhythmia. Thus, Orning[8] and Hellestrand et al.[12] found a marked slowing of conduction in accessory pathways in patients with Wolff-Parkinson-White syndrome and AV nodal reentrant tachycardia. The drug was extremely effective in the acute management of these tachyarrhythmias. The increase in atrial refractory periods in this study, together with a slowing of intraatrial conduction,[13] effected by flecainide acetate, also suggests a therapeutic potential of the drug in supraventricular tachyarrhythmia.

We found a small (5%) but significant increase in Q-T_{100} after administration of flecainide acetate. However, the observed Q-T prolongation is not as large as is usually found with other class I antiarrhythmic drugs such as quinidine[27] and can largely be explained by the QRS prolongation.

In view of our findings, we conclude that flecainide acetate prolongs intracardiac conduction and refractory periods in the atrium, AV node, and ventricle, and thus it appears to be a potentially effective antiarrhythmic drug. It did not alter spontaneous heart rate. However, the drug depresses sinus nodal function in patients with sinus nodal dysfunction and should be used with caution in such patients.

Acknowledgment

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Epicardial Activation of the Human Ventricle: Effects of Left Ventricular Hypertrophy

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To determine the effects of left ventricular hypertrophy on epicardial activation of the human heart, intraoperative epicardial mapping of 40 to 66 points was performed in 10 patients undergoing aortic valve replacement. Mean calculated left ventricular mass was 364 ± 98 g. All patients had normal left ventricular contraction. Earliest epicardial activation occurred in the anterior right ventricle in all patients. In 9 patients, it was the only epicardial breakthrough point. One patient had a single inferior left ventricular breakthrough point. Epicardial activation spread from the right ventricle towards the left ventricle in both the anterior and inferior direction. Latest epicardial activation occurred at the base of the left ventricle in 9 patients and the base of the right ventricle in 1.

When compared with patients with coronary artery disease, normal ventricular contraction, and no left ventricular hypertrophy, patients with hypertrophy had fewer left ventricular breakthrough points ($p < 0.001$) and were more likely to have latest activation at the left ventricular base ($p < 0.001$).

We conclude that left ventricular hypertrophy is associated with marked changes in the pattern of epicardial activation. These changes may reflect delay in spread from endocardium due to the increased wall thickness.

The spread of electrical activation through the human heart has been studied both in reperfused hearts and by electrical mapping at surgery.[1–3] We recently described the changes in epicardial activation that occur in patients with coronary artery disease and regional contraction abnormalities.[4] In this report we present the results of epicardial mapping in patients with left ventricular hypertrophy.

Methods

Patients: Epicardial mapping was performed in 10 patients undergoing aortic valve replacement. The clinical and electrocardiographic features of the patients are summarized in Table I. There were 6 male and 4 female patients with a mean age of 65 ± 11 years. Seven patients had predominant aortic stenosis and 3 had predominant aortic insufficiency. An intraventricular conduction defect, acute myocardial infarction, or acute ischemic syndrome was not present in any patient, and no patient was receiving antiarrhythmic medication.

Preoperative evaluation: All patients underwent diagnostic quality echocardiography and diagnostic cardiac catheterization preoperatively. Left ventricular mass was calculated from the echocardiographic measure of septal and left ventricular posterior wall thickness according to the formula of Devereux and Reichek.[5] Regional wall motion as analyzed by ventriculography was normal in all patients.

Epicardial mapping: Patients were operated on through a median sternotomy. Mapping was performed during stable sinus rhythm, after cannulation of the great vessels but before institution of cardiopulmonary bypass. Simultaneous recordings were made of 3 body surface electrocardiogram leads, a bipolar reference ventricular electrogram, and a bipolar electrogram from the exploring probe. The reference electrode consisted of 2 stainless steel suture electrodes attached to the anterior right ventricular wall. The roving electrode consisted of 2 electrodes that were 2 mm apart and embedded in a plastic mesh.

Bipolar electrograms were recorded from 40 to 66 predetermined epicardial sites. Five to 15 right ventricular sites and 35 to 51 left ventricular sites were studied in each patient.

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TABLE I Clinical Electrocardiographic and Hemodynamic Characteristics

		Electrocardiography			Echocardiography				Catheterization		
Case	Age (yr) & Sex	LVH Voltage* (mm)	Strain	Axis	IVST (mm)	PWT (mm)	LVID (mm)	LVM_p (g)	AV Grad Mean (mm)	AI	CAD
1	59M	Present	−	+45	14	12	50	296.7	0	3+	LAD-85, RCA-80
2	65M	Present	+	0	18	15	54	468.3	74	2–3+	None
3	62M	Present	+	+45	12	12	75	460.8	0	2–3+	None
4	57M	Present	+	−45	13	13	49	278.9	94	0	None
5	67M	Present	+	+45	14	14	66	523.2	140	1+	None
6	75F	Absent	+	+90	15	15	40	275.9	45	1+	RCA-90
7	48M	Present	−	−15	12	12	70	434.8	5	4+	None
8	83F	Present	+	−10	14	13	45	259.7	110	3+	None
9	82F	Present	+	0	12	12	49	288.8	72	2–3+	None
10	57F	Absent	+	+30	12	12	59	355.0	48	2–3+	None

* Scott's criteria for left ventricular hypertrophy (LVH): RI + SIII (R wave amplitude lead I + S wave amplitude lead III) > 25 mm; R aVL >7.5 mm; R aVF >20 mm; S aVR >14 mm; SV_1 or V_2 + R V_5 or V_6 >35 mm; R V_5 or V_6 >26 mm; R + S (R + S wave amplitudes) in V lead >45 mm.

AI = aortic insufficiency; AV grad mean = mean aortic valve gradient; CAD = coronary artery disease (% stenosis); IVST = interventricular septal thickness; LAD = left anterior descending; LVM = left ventricular mass; LVID = left ventricular internal dimension; PWT = posterior wall thickness; RCA = right coronary artery.

Signals were isolated, amplified, and recorded at 200 mm/s paper speed on an Irex multichannel oscilloscopic recorder. Surface leads were recorded at 0.1 to 40 Hz and epicardial leads at 40 to 500 Hz. Heart rate and QRS morphology remained stable throughout the mapping period. Mapping was completed within 5 to 10 minutes in each patient. There was no morbidity from the mapping procedure.

Measurements were performed from the peak of the major deflection of the reference electrogram to the peak of the major deflection of the electrogram from the roving electrode. The interval from the earliest onset of the QRS in the body surface leads to the reference electrogram was added to the interval from the reference electrogram to the roving electrogram to determine local activation time. Local activation times were calculated as the mean of 5 to 10 beats in stable sinus rhythm. Measurements were considered accurate to ± 5 ms, and measurements on individual beats at a given site were always within the range.

Epicardial breakthroughs were defined as sites of emergence of a radially propagating wave front at the epicardial surface, providing an island of early activation, completely surrounded by points of later activation. Latest epicardial activation was considered the site of latest recordable ventricular activation.

Comparison with patients without hypertrophy: To delineate changes due to left ventricular hypertrophy, we compared our present findings with our previously published data from 9 patients with coronary artery disease and normal ventriculograms.[4] None of these patients had any clinical, electrocardiographic, or echocardiographic evidence of left ventricular hypertrophy nor was the left ventricle thickened at surgery. In these 9 patients, earliest epicardial breakthrough site was the anterior right ventricle, followed by 2 left ventricular breakthrough sites, 1 in the anterior left ventricle and 1 in the inferior left ventricle in each patient. The latest epicardial activation site was located at the base of the right ventricle in 7 patients and at the base of the left ventricle in 2 patients.

Results

Echocardiographic and catheterization findings: Echocardiographic and catheterization findings are summarized in Table I. Seven patients had aortic stenosis and 3 had aortic regurgitation. All patients had increased wall thickness on echocardiography with septal and posterior wall thickness of 12 to 18 mm and 12 to 15 mm, respectively. Left ventricular mass as calculated from the echocardiogram ranged from 260 to 523 g (mean 364 ± 98).

Electrophysiologic findings: Epicardial electrograms from a patient with left ventricular hypertrophy

TABLE II Electrophysiologic Variables

			EBT (Site/Onset [ms])			
Case	Age (yr) & Sex	QRS (ms)	1st	2nd	3rd	LEA (Site/Onset [ms])
1	59M	95	ARV (15)	. . .	. . .	ARV base (62)
2	65M	85	ARV (20)	. . .	. . .	ILV base (70)
3	62M	110	ARV (8)	. . .	. . .	ILV base (80)
4	57M	95	ARV (25)	ILV (45)	. .	ALV base (83)
5	67M	80	ARV (13)	. . .	. . .	LLV base (69)
6	75F	75	ARV (13)	. . .	. . .	ILV base (63)
7	48M	85	ARV (14)	. . .	. . .	LLV base (85)
8	83F	100	ARV (14)	. . .	. . .	LLV base (85)
9	82F	85	ARV (4)	. . .	. . .	LLV base (85)
10	57F	75	ARV (20)	. . .	. . .	ILLV base (70)

ALV = anterior left ventricle; ARV = anterior right ventricle; EBT = early breakthrough site; ILLV = inferolateral left ventricle; IVL = inferior left ventricle; LLV = lateral left ventricle.

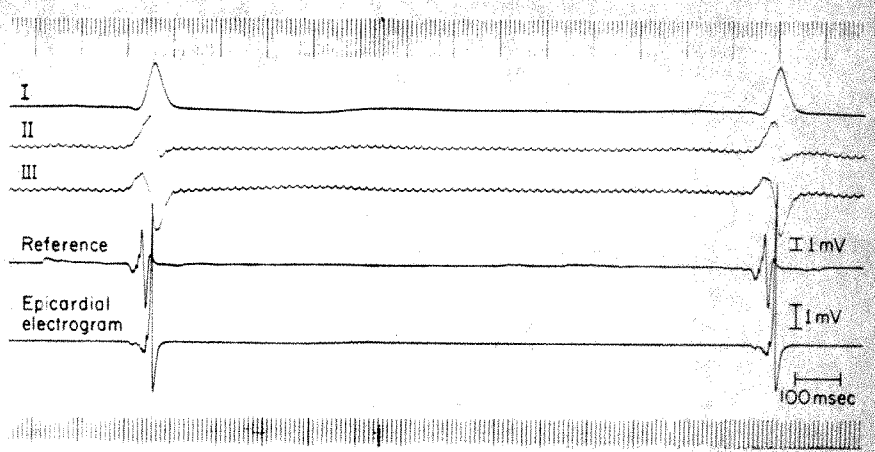

FIGURE 1. Epicardial electrogram from a patient with left ventricular hypertrophy. Three surface leads, a reference electrogram from the right ventricle, and a bipolar electrogram from the roving probe are recorded simultaneously.

are illustrated in Figure 1. A complete epicardial map of a patient with left ventricular hypertrophy is illustrated in Figure 2. Electrophysiologic data from all 10 patients are summarized in Table II.

Epicardial breakthrough: Each patient had the earliest epicardial breakthrough in the anterior paraseptal right ventricle. In 9 patients with hypertrophy this site was the only epicardial breakthrough point and there were no left ventricular breakthrough sites. One of the 10 patients with hypertrophy had a second breakthrough on the inferior surface of the left ventricle, which compares with 1 right ventricular and 2 left ventricular breakthrough sites in 9 of 9 patients without hypertrophy. When compared with patients without hypertrophy, patients with left ventricular hypertrophy had fewer left ventricular breakthrough points ($p < 0.001$).

Latest epicardial activation: Latest epicardial activation occurred at the base of the left ventricle in 9 patients and at the base of the right ventricle in 1, which compares with the base of the left ventricle as the latest activation site in 2 of 9 patients without hypertrophy ($p < 0.001$).

Spread of activation: Activation of the left ventricle occurred after activation of the right ventricle in all patients. The anterior left ventricle was activated after the anterior right ventricle, and the inferior left ventricle was activated after the inferior right ventricle.

Correlation of mapping and electrocardiographic findings: Mapping findings were not related to electrical axis, voltage, or presence of a strain pattern on electrocardiogram.

Discussion

Durrer et al.[1] defined the spread of activation through the human heart by detailed epicardial and intramural mapping of hearts extirpated from victims of automobile accidents. No patient had evidence of heart disease. The earliest endocardial activation sites were the paraseptal region at the base of the anterior papillary muscle, the central interventricular septum, and the paraseptal region at the base of the posterior papillary muscle. Activation spread in an endocardial to epicardial direction with epicardial breakthrough points on the anterior right ventricle, anterior paraseptal left ventricle, and posterior paraseptal left ventricle. Using intraoperative epicardial mapping, Wyndham et al.[3] in patients "without conduction defects" and we[4] in patients with coronary artery disease without asynergy demonstrated that epicardial breakthrough occurred in the right ventricle followed by the anterior and inferior left ventricle.

Previous studies of activation in patients with left ventricular hypertrophy, recording unipolar leads from a few epicardial sites, demonstrated generalized delays in activation with large amplitude unipolar com-

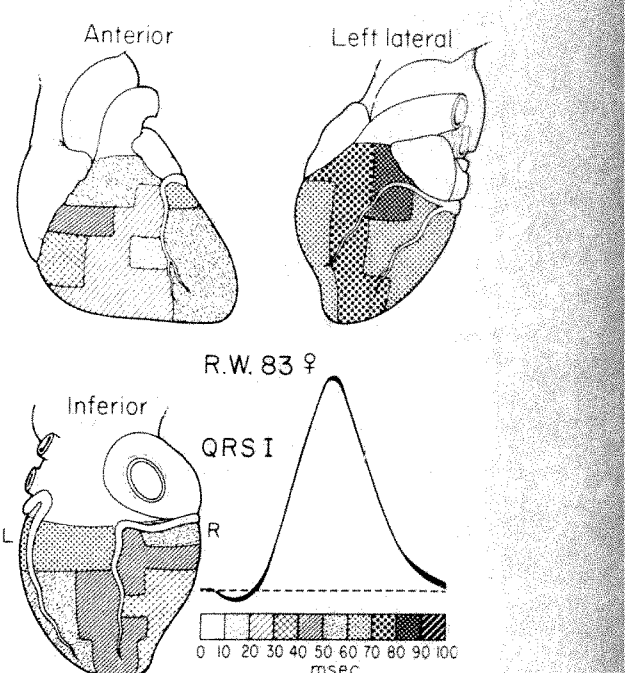

FIGURE 2. Epicardial map from a patient with left ventricular hypertrophy. Note a single epicardial breakthrough site on the anterior right ventricle. Activation spreads both anteriorly and inferiorly to the left ventricle. The latest activation site is the base of the lateral left ventricle.

plexes.[6,7] Wyndham et al.[8] described epicardial activation in a single patient with left ventricular hypertrophy, as seen at surgery. They found normal right ventricular breakthrough sites but none on the left. The left ventricle was activated by anterior and inferior spread from the right ventricle. The latest epicardial activation site was the base of the left ventricle. Animal[9,10] and human[11,12] studies have demonstrated delayed epicardial activation of the right ventricle in right ventricular hypertrophy.

Our study is the first to systematically examine the pattern of epicardial activation in patients with left ventricular hypertrophy. We found that left ventricular hypertrophy is associated with marked reduction in left ventricular epicardial breakthrough sites. Epicardial activation appears to spread anteriorly and inferiorly from the right ventricle. Latest epicardial activation generally occurs at the lateral base of the left ventricle.

These alterations may be due to delay in endocardial to epicardial conduction in hypertrophied muscle. Such delay would allow for fusion of activation from adjacent areas and elimination of discrete epicardial breakthrough. Delay of spread through the thickened left ventricle would cause the left ventricular base to be activated after the right ventricular base.

An alternative explanation for our findings is the hypothesis of Piccolo et al.[13] that electrocardiographic changes in left ventricular hypertrophy are due to coexisting disease in the bundle branch system. Wyndham et al.[14] showed that in the presence of left anterior hemiblock there are no anterior left ventricular breakthrough sites and in the presence of left bundle branch block there are no left ventricular breakthrough sites.[8] Thus, some form of bundle branch delay might explain the absence of left ventricular breakthrough points in patients with hypertrophy. We think this explanation is less likely, especially because our findings were consistent in patients with and those without left axis deviation.

We previously reported that epicardial breakthrough sites are absent in areas of akinesia and dyskinesia.[4] Thus, the changes that occur in areas of hypertrophy are similar to those seen in zones of asynergy. Our findings provide a baseline for the interpretation of abnormalities seen in patients with arrhythmia.

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Influence of the Autonomic Nervous System on the Q-T Interval in Man

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Drugs that affect the autonomic nervous system can influence the Q-T interval directly or by changing the heart rate. Bazett's formula to correct for rate may be misleading after certain drug interventions. This hypothesis was tested in 20 patients receiving both propranolol (0.15 mg/kg intravenously) and atropine (0.03 mg/kg intravenously). Six patients received propranolol first, 7 patients received atropine first, and 7 patients received atropine plus propranolol simultaneously. During control and after drug intervention, the Q-T interval was measured directly in sinus rhythm and during a fixed atrial paced rate, and was calculated using Bazett's formula. The ventricular effective refractory period was also determined in 6 patients after administration of atropine plus propranolol. The sinus cycle length (836 ± 156 to 648 ± 84 ms, mean ± standard deviation), measured Q-T interval (367 ± 26 to 329 ± 26 ms), and atrially paced Q-T interval (330 ± 28 to 315 ± 27 ms) shortened after atropine plus propranolol ($p < 0.001$), but the corrected Q-T interval with use of Bazett's formula did not change (402 ± 33 to 412 ± 24 ms). The ventricular effective refractory period also shortened from 241 to 20 to 218 ± 21 ms after atropine plus propranolol ($p < 0.02$). The sinus cycle length increased after propranolol (750 ± 97 to 907 ± 108 ms, $p < 0.001$), but no change occurred in the measured Q-T interval or atrial paced Q-T interval although the corrected Q-T interval using Bazett's formula was greatly shortened (428 ± 15 to 391 ± 22 ms, $p < 0.001$). The sinus cycle length, measured Q-T interval, and atrially paced Q-T interval decreased after atropine ($p < 0.01$), but the corrected Q-T interval lengthened (375 ± 29 to 418 ± 28 ms, $p < 0.01$).

***In summary*, atropine and atropine plus propranolol shorten the Q-T interval independent of rate, demonstrating a direct vagal effect on the Q-T interval. Bazett's formula inaccurately predicts the Q-T interval after administration of atropine, propranolol, and atropine plus propranolol.**

The Q-T interval is an approximate measure of myocardial depolarization and repolarization and, like ventricular refractoriness,[1] is influenced by changes in heart rate.[2,3] Measures to correct for heart rate have included formulas derived by Bazett[3] and others.[4,5] However, drugs that alter both heart rate and ventricular refractoriness might have a complex effect on the Q-T interval. Formulas to correct for heart rate during application of these drugs may yield erroneous results for the Q-T interval. For example, although propranolol appears to shorten the Q-T interval after the changes in heart rate that it produces are corrected by Bazett's formula,[6,7] recent data[8,9] suggest that when the rate is held constant by atrial pacing during administration of propranolol, the Q-T interval does not shorten.

Recently, we[10] demonstrated that atropine or atropine and propranolol shortened the ventricular effective refractory period in man, measured with programmed stimulation of the right ventricle. However, the effects of atropine and the combination of atropine and propranolol on the Q-T interval have not been reported. The purpose of this study was threefold: (1) to determine the effects of atropine, propranolol, and atropine plus propranolol on the Q-T interval during fixed-rate atrial pacing; (2) to compare these Q-T measurements with those corrected for rate using Bazett's formula[3]; and (3) to correlate these findings with measurement of ventricular refractoriness determined with programmed ventricular stimulation.

Methods

Study patients: Twenty patients undergoing electrophysiologic study were selected prospectively for autonomic manipulation (Table I). Requirements for selection were that the patient (1) had no contraindication to intravenous administration of propranolol (0.15 mg/kg body weight) and

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TABLE I Patient Characteristics

Case	Age (yr) & Sex	Heart Disease	Diagnosis
1	31M	None	Repetitive monomorphic VT[21]
2	62M	CAD	VT
3	22F	MVP	VT
4	53F	None	VT
5	61M	CAD	VT
6	50M	None	Syncope
7	56M	None	Sinus bradycardia
8	33M	None	Episodic Mobitz type I AV block
9	15M	None	Episodic Mobitz type I AV block
10	32M	None	Sinus bradycardia
11	61F	None	VT
12	30M	None	Paroxysmal SVT
13	21F	None	Sick sinus syndrome
14	27F	None	Frequent PVC, palpitation
15	39M	None	Sick sinus syndrome
16	33F	None	VT
17	57F	CAD	VT
18	29F	MVP	VT
19	40M	MVP	VT
20	19F	None	VT

AV = atrioventricular; CAD = coronary artery disease; MVP = mitral valve prolapse; PVC = premature ventricular complexes; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

atropine (0.03 mg/kg), (2) had ventricular complexes with a QRS duration of 100 ms or less, (3) had clearly discernible T waves, and (4) gave written informed consent for the study. Patients whose U wave merged with the T wave were excluded.

All patients underwent complete electrophysiologic study, details of which may be found elsewhere.[10,11] In all patients the Q-T interval was measured in complexes generated during atrial pacing at the high right atrium. Ventricular refractoriness was determined during pacing at the right ventricular apex using the same pacing cycle length before and after drug administration. Electrocardiographic leads I, II, III, and V_1 were recorded simultaneously throughout the study.

Q-T measurement: For each patient, the lead in which the Q-T interval was seen best was used before and during drug interactions. The Q-T interval was measured from the onset of the Q (or R) wave to the termination of the T wave, which was determined by the intersection of a tangent drawn to the steepest slope of the downsloping portion of the T wave and the isoelectric baseline.[2] During atrial pacing, 1:1 atrioventricular conduction was maintained and each cycle length was recorded for 8 or more complexes. The Q-T interval was measured in the last paced complex at the same paced rate and in the same lead before and during drug interventions. All measurements were done at a paper speed of 50 mm/s. The Q-T interval and ventricular refractory period measurements were done by separate investigators who were blinded to each others' data.

Autonomic blockade: For each patient atropine and propranolol were administered only after completing the control part of the electrophysiologic study, including programmed atrial and ventricular stimulation. Propranolol, 0.15 mg/kg, was given intravenously at 1 mg/min. Atropine, 0.03 mg/kg, was administered intravenously during a period of 3 minutes. The doses used have been shown to block effectively the influence of the autonomic nervous system on sinus nodal automaticity,[12,13] the effect of isoproterenol on ventricular refractoriness,[10] and the effect of vagal-induced changes on atrial refractoriness and sinus nodal automaticity.[14,15] The entire autonomic pacing protocol always was finished in less than 30 minutes.

All patients received both atropine and propranolol. In 6 patients propranolol was given first and electrophysiologic data were collected. These patients then received atropine and had the pacing studies repeated. Seven patients were given atropine first, and after the pacing studies were performed propranolol was given and pacing was repeated. Six patients received atropine and propranolol simultaneously, and electrophysiologic measurements were obtained only in the presence of both drugs.

Definitions: Q-T measured (Q-Tm) refers to Q-T intervals measured during sinus rhythm and 1:1 atrioventricular conduction. The mean of 10 complexes at a sinus rate that varied less than 5% was used. Q-T corrected (Q-Tc) refers to Q-T measured data that has been corrected for rate using Bazett's method; that is, $Q\text{-}Tc = Q\text{-}Tm/\sqrt{\text{sinus cycle length}}$. Q-T paced (Q-Tp) refers to the measured Q-T interval during constant atrial pacing. Sinus cycle length is the time in seconds between the P waves of 2 successive complexes. The sinus cycle length used in the calculation was the mean of 10 consecutive intervals.

Statistics: Statistical evaluation was performed on all measured and calculated points. Paired t analysis was used to compare effect of the drug on each measured interval. Analysis of variance was used when more than 2 groups were compared. Comparison of change from control was done by paired t test adjusted for multiple comparisons.[16]

Results

Patient groups: The patients were classified into 3 groups. All patients who received both propranolol and atropine constitute Group I (n = 20). Group II (n = 6) was a subset of Group I and included patients who received propranolol first followed by atropine. Group III (n = 7) was also a subset of Group I and represented patients who received atropine first followed by propranolol. Seven patients were given propranolol and atropine concomitantly. Patient characteristics are noted in Table I. Fourteen patients had no heart disease, 3 had coronary heart disease, and 3 had mitral valve prolapse. "No heart disease" was defined as no detectable structural heart disease identified by physical examination, electrocardiography, echocardiography, and left heart catheterization and coronary angiography.

Measured and paced Q-T interval: Table II and Figure 1 show the Q-T interval data during sinus and paced rhythm for all groups. Propranolol significantly ($p < 0.001$) increased the sinus cycle length in all Group II patients, but the mean measured Q-T interval changed insignificantly from 380 ± 18 to 372 ± 23 ms. In contrast, atropine significantly ($p < 0.01$) decreased sinus cycle length in all Group III patients and significantly shortened the mean measured Q-T interval from 360 ± 21 to 306 ± 24 ms ($p < 0.001$). After administration of propranolol plus atropine (Group I) the sinus cycle length decreased in all patients (836 ± 156 to 648 ± 84 ms, $p < 0.001$) and the mean measured Q-T interval shortened from 367 ± 26 to 329 ± 26 ms ($p < 0.001$).

TABLE II Q-T Interval Data (ms)

	Sinus Cycle Length				Q-T Measured				Q-T Corrected				Q-T Paced			
Case	C	P	A	A&P	C	P	A	A&P	C	P	A	A&P	PCL	C	P	A	A&P
1	720	870	...	640	385	330	...	295	400	355	...	370	500	300	315	...	290
2	800	890	...	760	385	375	...	340	430	400	...	390	500	350	350	...	330
3	870	1075	...	530	400	400	...	325	430	385	...	445	400	310	310	...	305
4	720	810	...	630	370	380	...	350	435	410	...	440	500	380	350	...	340
5	820	950	...	710	390	370	...	355	430	380	...	420	500	360	385	...	350
6	620	830	...	550	350	380	...	325	445	415	...	440	500	350	360	...	330
7	770	...	730	660	330	...	320	315	375	...	375	390	500	330	...	300	290
8	765	...	480	625	350	...	290	315	400	...	420	400	500	330	...	290	300
9	1060	...	510	710	350	...	290	310	340	...	405	370	600	330	...	285	300
10	1270	...	645	780	370	...	325	345	330	...	405	390	500	330	...	320	320
11	915	...	550	830	390	...	345	390	405	...	465	430	400	340	...	330	330
12	715	...	450	605	330	...	285	310	390	...	425	400	400	290	...	275	275
13	920	...	490	590	370	...	300	320	385	...	430	415	500	330	...	310	325
14	580	...	...	540	335	...	...	300	440	...	...	410	500	320	...	...	305
15	960	...	...	695	360	...	...	315	365	...	...	380	500	320	...	...	295
16	890	...	...	515	365	...	...	280	385	...	...	390	400	280	...	...	265
17	770	...	...	660	375	...	...	365	425	...	...	450	500	360	...	...	355
18	960	...	...	645	430	...	...	355	440	...	...	440	500	380	...	...	370
19	830	...	...	670	365	...	...	330	400	...	...	440	500	380	...	...	330
20	760	...	...	610	350	...	...	340	400	...	...	435	400	280	...	...	290
Group	I C	II C/P	III C/A	I A&P	I C	II C/P	III C/A	I A&P	I C	II C/P	III C/A	I A&P		I C	II C/P	III C/A	I A&P
X	836	750/907	916/551	648	367	380/372	360/306	329	402	428/391	375/418	411		330	338/345	376/301	315
SX	156	97/108	196/101	84	26	18/23	21/24	26	33	15/22	29/28	26		28	26/28	16/15	27
p	...	<0.001	<0.01	<0.001	...	NS	<0.001	<0.001	...	<0.001	<0.01	NS		...	NS	<0.01	<0.001

Group I (n = 20) = patients who received atropine and propranolol; Group II (n = 6) = patients who received propranolol first; Group III (n = 7) = patients who received atropine first. A = atropine; A&P = atropine and propranolol; C = control; P = propranolol; p = Student's paired *t* test; PCL = paced cycle length; Q-T corrected = Q-Tm/√ sinus cycle length; Q-T measured = measured Q-T interval at the listed sinus cycle length; Q-T paced = measured Q-T interval at the listed paced cycle length; SX = standard deviation of X; X = arithmetic mean.

Corrected Q-T interval versus fixed atrial pacing: To allow for rate-independent Q-T interval assessment, we used Bazett's method and atrial pacing at a fixed cycle length. In Group II patients, the Q-T shortened from 428 ± 15 to 391 ± 22 ms ($p < 0.001$) using Bazett's method but did not change during atrial pacing (338 ± 28 to 345 ± 28 ms, difference not significant [NS]). The Q-T interval during atropine administration (Group III) significantly lengthened from 375 ± 29 to 418 ± 28 ms ($p < 0.01$) using Bazett's method, but substantially shortened from 376 ± 16 to 301 ± 15 ms ($p < 0.01$) during fixed atrial pacing. For all patients (Group I), propranolol plus atropine resulted in no change in the Q-T interval using Bazett's method (402 ± 33 to 411 ± 26 ms, p = NS). However, during atrial pacing the Q-T interval significantly shortened (330 ± 28 to 315 ± 27 ms, $p < 0.001$) in Group I patients. The changes from control in Q-T intervals during drug therapy are shown in Figure 1.

Ventricular effective refractory period: In 6 patients the ventricular effective refractory period was determined at the same paced cycle length as atrial pacing before and after administration of atropine plus propranolol, and the changes from control are depicted in Figure 1. For these patients the control ventricular effective refractory period was 241 ± 20 ms, and it decreased to 218 ± 21 ms ($p < 0.02$) after administration of atropine and propranolol. During atrial pacing the change in Q-T interval measured during atrial pacing after propranolol plus atropine administration was

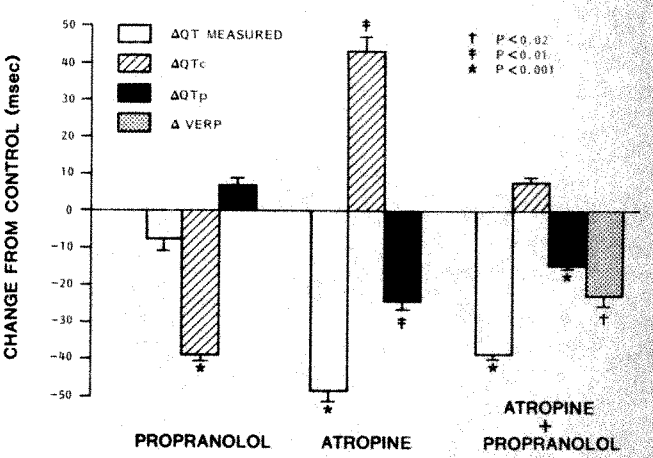

FIGURE 1. Effect of atropine and propranolol on Q-T interval. The change from control in the mean Q-T interval is plotted for each drug intervention. The change in corrected Q-T interval using Bazett's method occurs in the opposite direction than either measured or paced Q-T interval data. The direction of change in ventricular effective refractory period after atropine plus propranolol administration is similar to measured and paced Q-T interval changes. ΔQ-T measured = measured Q-T interval after drug minus measured Q-T interval during control; ΔQ-Tc = ΔQ-T measured corrected for rate using Bazett's method; ΔQ-Tp = Q-T interval at a fixed atrial pacing rate after drug minus Q-T interval at the same atrial pacing rate during control; ΔVERP = ventricular effective refractory period after drug minus ventricular effective refractory period during control. Significance levels refer to changes from control.

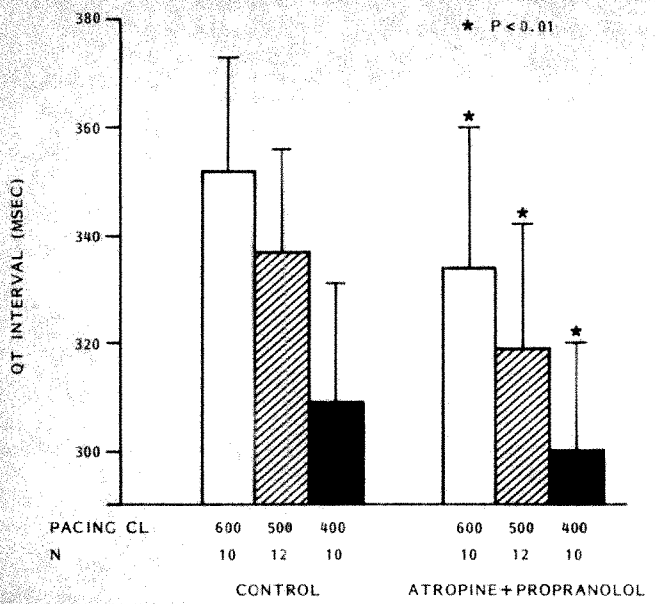

FIGURE 2. Change in Q-T interval after administration of atropine and propranolol as a function of heart rate. Each group was paced at the listed pacing cycle length (CL). The Q-T interval significantly ($p < 0.01$) shortened from control in each group after administration of atropine plus propranolol. The magnitude of change for each pacing rate is similar to the magnitude of change at any other pacing rate.

consistent with the changes in ventricular refractoriness. However, the Q-T interval corrected for rate by Bazett's formula increased rather than decreased when atropine and propranolol were given. Similar discordance between the Q-T interval measured during atrial pacing and calculated using Bazett's formula was noted during single drug intervention with either propranolol or atropine (Fig. 1).

Role of pacing rate: Although all Q-T measurements during atrial pacing were made at the same atrial pacing rate before and during drug intervention, the rate varied among patients. Figure 2 shows the mean data for Group I patients at paced rates of 600, 500, and 400 ms. Statistical analysis of the change in Q-T interval at each rate during drug intervention demonstrated no difference among the 3 rates used (that is, the magnitude of change in the Q-T interval from the control value was similar regardless of the rate tested).

Discussion

Bazett's formula for correcting the Q-T interval for heart rate: Our data clearly depict the difficulty in using a correction factor to assess Q-T interval when evaluating drugs that affect both heart rate and Q-T interval. This problem was first noted in Bazett's original report[3] in 1920. Using his formula $Q\text{-}T = K\sqrt{\text{R-R interval}}$, Bazett calculated the effect of sectioning the vagus in dogs from data collected by Einthoven[17] in 1908. He found that the K value increased after vagal section and decreased with vagal stimulation. Since that time a number of formulas have been developed to reflect more accurately the change in Q-T interval caused by heart rate.[2,4,5,18–20] No formula has been developed to permit assessment of drug effect on the Q-T interval. Simonson et al.[4] further defined the relation of the Q-T to the R-R interval and found that it also was related to the patient's age. He stated that all currently used formulas were applicable only between rates of 50 to 115 complexes/min and that the effect of exercise on Q-T interval was unknown. Recently, atrial pacing to fix the heart rate has been used to evaluate the changes in Q-T interval caused by propranolol. It was shown that Bazett's formula predicted a shortening in Q-T interval, although at identical atrial pacing rates the Q-T interval did not change significantly.[8,9]

Correction for the Q-T interval using Bazett's formula proved misleading when either atropine or propranolol was given. Atropine actually significantly shortens the Q-T interval measured during atrial pacing, whereas Bazett's formula predicts that the Q-T interval lengthens when corrected for rate. Atropine also shortens the ventricular effective refractory period.[10] In addition, both propranolol and propranolol plus atropine produced measured Q-T intervals inconsistent with those predicted by Bazett's formula.

Role of atrial pacing: Atrial pacing permits comparison of ventricular changes in depolarization and repolarization without relying on a rate correction formula. Bazett's formula has been shown to be unreliable at slow or fast heart rates.[4] Propranolol significantly slowed the heart rate and atropine significantly increased the heart rate. Additionally, atropine had a direct effect on shortening on Q-T interval. These factors, in combination with other effects, may contribute to the differences found between the Q-T interval measured during pacing and the Q-T interval corrected for rate by Bazett's formula.

The ventricular effective refractory period, an independent measure of repolarization, was determined in 6 patients before and after atropine and propranolol administration. The changes in refractoriness mirrored the change in paced Q-T interval but was discordant with the change in corrected Q-T interval using Bazett's formula. It has previously been shown that the ventricular effective refractory period does not change when propranolol is given but shortens with administration of atropine and atropine plus propranolol.[10] These data totally agree with the paced Q-T data, indirectly corroborating the drug effects on ventricular repolarization noted in this study.

Implications: The Q-T interval is the electrocardiographic approximation of ventricular depolarization and repolarization throughout the heart and may not accurately reflect individual electrophysiologic changes in all areas of the ventricles. Thus, although autonomic blockade shortened both Q-T interval and right ventricular refractoriness at the apex, it is possible that ventricular refractoriness did not change or even lengthened at other ventricular sites, such as those af-

fected by regional ischemia or scar due to tissue inhomogeneity. This limitation applies to all studies in which the effect of a drug or other intervention is tested at only 1 site, the usual method used in man.

In conclusion, resting parasympathetic tone appears to affect directly the Q-T interval in man, and withdrawal of vagal tone shortens the Q-T interval. Further, vagal influence on the ventricle as measured by change in the Q-T interval may be measured from the surface electrocardiogram only when the heart rate is fixed as in atrial pacing. Bazett's formula may be misleading when applied to drugs that affect both heart rate and Q-T interval directly.

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Subcostal M-Mode Echocardiography of the Right Atrial Wall in the Diagnosis of Cardiac Arrhythmias

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The M-mode echocardiogram of the right atrial (RA) wall can be easily recorded in each person from the subcostal location. In a normal RA wall motion pattern, atrial contraction is represented by a markedly prominent posterior motion. The presence or absence of atrial contractions in the subcostal RA wall echocardiogram, their amplitude, and their timing may help in the diagnosis of cardiac arrhythmias with the simultaneously recorded nondiagnostic electrocardiogram. Flat and hidden P waves can be accurately identified throughout the cardiac cycle. It is possible to distinguish between atrial, ventricular, and nodal premature beats and to recognize atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia, paroxysmal atrial tachycardia with block, atrioventricular (AV) nodal tachycardia, and supraventricular tachycardias with aberrant ventricular conduction. The diagnosis of wandering pacemaker, AV dissociation, sinoatrial block, and AV block is facilitated.

On the basis of study of 60 patients with various rhythm disturbances, it was concluded that analysis of the subcostal RA wall echocardiogram is a new, helpful noninvasive approach in the diagnosis of cardiac arrhythmias.

Several echocardiographic studies[1–8] have assessed the applicability of M-mode echocardiography in the analysis of cardiac arrhythmias. It has been demonstrated that the abnormalities associated with the motion of various cardiac structures could have diagnostic implications in certain rhythm disturbances. However, the subcostal RA wall echocardiogram has not been used in the detection of cardiac arrhythmias. The purpose of this report is to describe the advantages of analyzing RA wall motion patterns in subcostal M-mode recordings to aid in the diagnosis of cardiac arrhythmias.

Methods

Patients: Sixty patients with various rhythm disturbances were studied by electrocardiography and subcostal M-mode echocardiography. Intracardiac electrophysiologic studies were also carried out in a few patients. The electrocardiogram revealed sinus arrhythmia and wandering pacemaker in 8, atrial, ventricular, and atrioventricular (AV) nodal premature beats in 20, atrial fibrillation in 10, atrial flutter in 6, AV nodal rhythm, supraventricular paroxysmal tachycardia, and atrial tachycardia with block in 8, sinoatrial block in 2, and AV dissociation and various degrees of AV block in 16 patients.

Echocardiography: Echocardiograms were performed with a commercially available ultrasonic device utilizing the 2.25 MHz transducer. Lead II of the electrocardiogram and occasionally a phonocardiogram were recorded simultaneously. The paper speed was 2.5, 5, and 7.5 cm/s.

The transducer was placed in the subxiphoid area slightly to the patient's right and directed toward the middle of the right clavicle. The RA wall is easily recorded from this location in each person. Slight changes of the transducer angulation are then necessary to obtain maximal atrial wall motion amplitude, but the recording should be made under the constant angle of the ultrasonic beam.

Results

Normal right atrial motion: While performing the subcostal M-mode study in patients with transvenous right ventricular pacing catheters, it was observed that the RA wall can be easily and quickly recorded in each patient.[9] This was later confirmed in more than 150 routine echocardiographic examinations.

Normal right RA wall motion has a characteristic pattern in a subcostal M-mode echocardiogram. The wall moves anteriorly during ventricular systole, at

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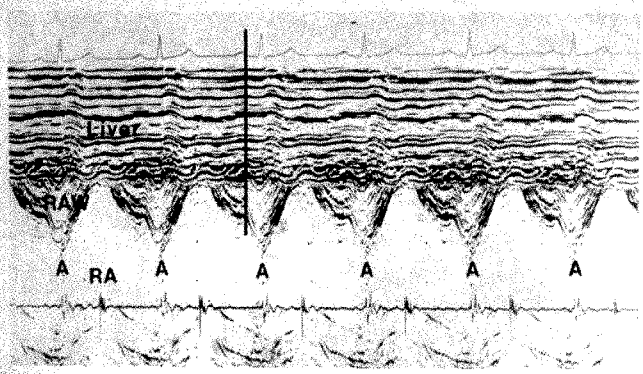

FIGURE 1. Subcostal M-mode echocardiogram of the right atrial wall (RAW) in a normal subject. Atrial contractions (A) start at the nadir of the P wave and before the first heart sound. RA = right atrium.

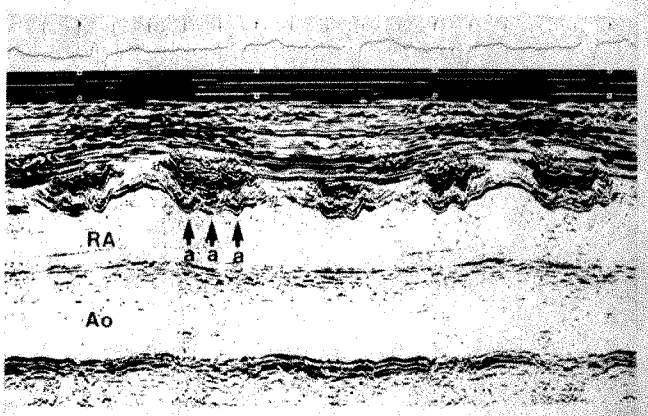

FIGURE 2. Subcostal right atrial wall echocardiogram in a patient with coarse atrial fibrillation waves on the electrocardiogram. Their counterparts in the echocardiogram are small amplitude atrial contractions (a). Ao = aorta; RA = right atrium.

which time the tricuspid valve is closed and the right atrium fills with blood. With the opening of the tricuspid valve, the RA wall rapidly moves posteriorly. A plateau occurs throughout the remaining ventricular diastole ending with atrial contraction that is presented as a prominent posterior motion (Fig. 1). Atrial contraction starts on the nadir of the P wave in the electrocardiogram and cannot be mistaken for the right ventricular wall contraction that begins at the nadir of the R wave.

The presence or absence of atrial contractions in a subcostal right atrial wall echocardiogram, their amplitude, and their timing might help in the diagnosis of cardiac arrhythmias in doubtful cases with nondiagnostic electrocardiograms. Each arrhythmia has a specific RA wall motion pattern.

Atrial fibrillation and flutter: Atrial fibrillation is characterized by the absence of atrial contraction. Fine atrial fibrillation does not cause any significant oscillatory movement in the right atrial wall echocardiogram. In contrast, coarse fibrillary waves are demonstrated as small amplitude atrial contractions, usually better visualized during ventricular diastole (Fig. 2).

Figure 3 illustrates the echocardiographic pattern of atrial flutter with a 2:1 atrioventricular block. Flutter waves are not discernible in the electrocardiogram because of superimposed QRS and T waves. On the contrary, flutter contractions and their rate (320/min) are clearly demonstrated in the RA wall echocardiogram.

Premature beats: Figure 4 shows an atrial premature beat with aberration of the QRS. The P wave is superimposed on the peak of the T wave of the preceding beat, and this is well documented by an atrial contraction in the RA wall echocardiogram. Similarly, the P waves lost in the T waves and QRS complex can be easily detected in the subcostal RA echocardiogram, as seen in the example of a patient with a functioning ventricular pacemaker (Fig. 5).

The echocardiographic pattern of 2 nodal beats is illustrated in Figure 6. It is obvious that the atrium and

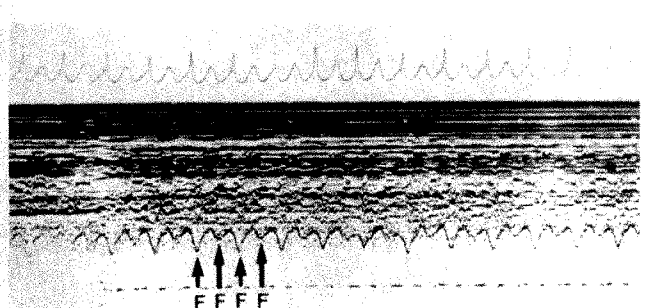

FIGURE 3. Subcostal RA wall echocardiogram of a patient with atrial flutter. Flutter contractions (F) are clearly visible and are of higher amplitude than fibrillatory contractions. Contractions indicated with **long arrows** are of small amplitude when occurring during ventricular systole.

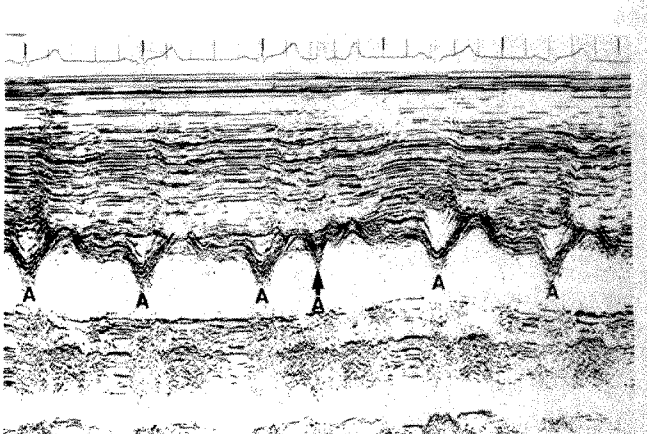

FIGURE 4. Subcostal RA wall echocardiogram of a patient in sinus rhythm and ectopic atrial beat with aberrant ventricular conduction. Fourth P wave is premature and indistinct because of superimposition on the T wave of the preceding beat. It is well recognized in the echocardiogram by the presence of a premature atrial contraction (**arrow**). A = atrial contraction.

ventricle contract simultaneously. As can be seen from the distorted atrial filling curve, an abortive atrial contraction occurs during ventricular systole. At the same time, atrial filling diminishes considerably. The second beat is an atrial premature beat with aberrant ventricular conduction, as indicated by the preceding atrial contraction in the echocardiogram.

Recognition of a ventricular premature beat is more accurate in the atrial echocardiogram than in the electrocardiogram because the absence of the preceding atrial contraction can be better demonstrated (Fig. 7, top). Abortive atrial contraction is always visualized when a P wave of sinus origin is lost in the QRS of the ventricular extrasystole (Fig. 7, bottom). However, retrograde activation of the atria is highly probable if atrial contractions are premature and occur repeatedly at the same distance after ventricular extrasystoles.

Paroxysmal supraventricular tachycardia: Figure 8 (top) illustrates an unsuccessful attempt to terminate paroxysmal supraventricular tachycardia by right ventricular overdrive pacing. Supraventricular tachycardia is presented by the fast rate of atrial contractions that diminish in amplitude during pacing while the atrium contracts against the closed tricuspid valve. Atrial contractions caused by retrograde conduction on a 1:1 ratio always exhibit a characteristic zigzag pattern. Figure 8 (bottom) demonstrates the successful termination of atrial tachycardia in the same patient. After the interruption of pacing, sinus rhythm resumed as seen from the normal right atrial motion pattern.

Figure 9 illustrates the echocardiographic pattern of paroxysmal atrial tachycardia with 2:1 atrioventricular block. Some P waves are indistinguishable in the electrocardiogram, but all atrial contractions are visible in the echocardiogram. They are small in amplitude, particularly those occurring during ventricular systole and differ from flutter contractions in their rate. However, all contractions exhibit sufficient anterior motion to be recorded and no false-positive results were observed in any patient. Unlike sinus rhythm, the peak of the atrial contractions is simultaneous with the P waves. This probably occurs because of the altered distance between the ectopic focus and the recorded part of the right atrium.

AV dissociation and block: The practical value of the subcostal RA wall echocardiogram in detecting AV dissociation is demonstrated in Figure 10. Prompt recognition of independence between atrial and ven-

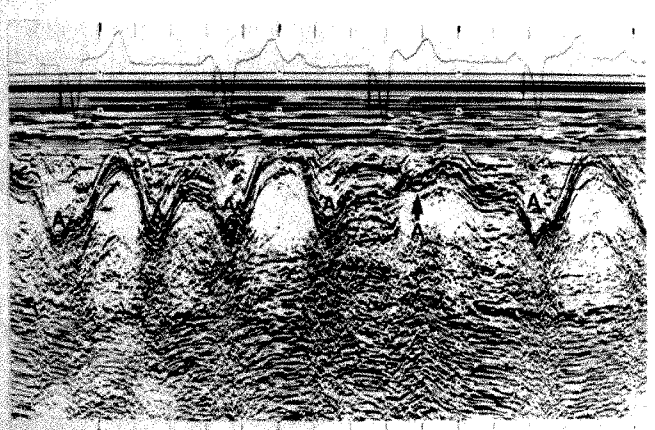

FIGURE 5. Subcostal echocardiogram of the RA wall of a patient with sinus rhythm and functioning ventricular pacemaker. P waves hidden in T wave and QRS complexes are recognized by corresponding atrial contractions (A). The fifth atrial contraction (**arrow**) has a small amplitude when occurring during ventricular systole.

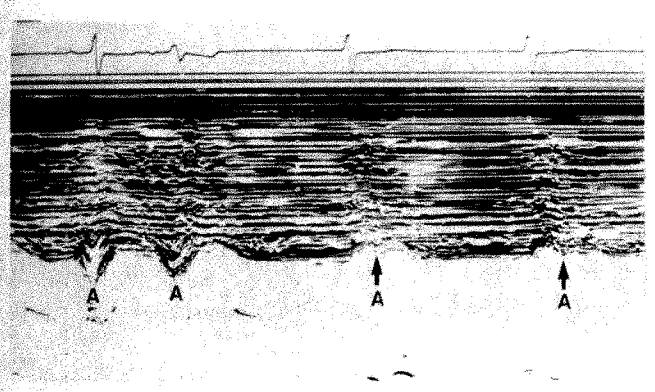

FIGURE 6. Subcostal RA wall echocardiogram in a patient with AV nodal rhythm. Nodal beats (third and fourth) are characterized by abortive atrial contraction (**arrow**) which occurs during ventricular systole. The second beat is preceded by atrial contraction and represents an atrial premature beat with aberrant ventricular conduction. A = atrial contraction.

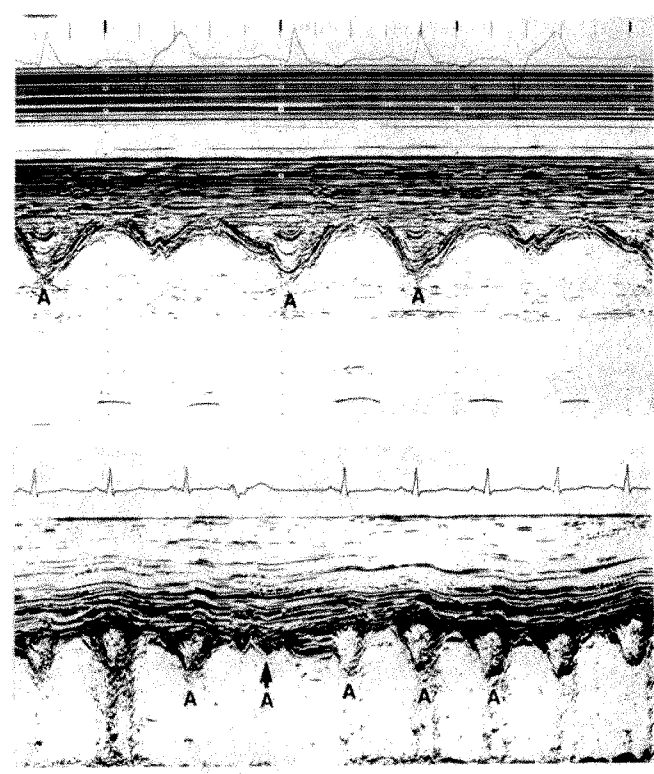

FIGURE 7. Top, subcostal RA wall echocardiogram of a patient in sinus rhythm with ventricular premature beats (second and fifth) which are recognized by the absence of preceding atrial contractions (A). **Bottom,** P wave hidden in the QRS of ventricular extrasystole presented as an abortive contraction (**arrow**).

tricular activity is possible because all atrial contractions are visible in the echocardiogram. Figure 11 presents a subcostal RA wall echocardiogram in a patient with complete AV block and sinus rhythm.

A subcostal RA wall echocardiogram might be helpful in studying the function of an implanted atrial pacemaker as seen in Figure 12, where improper atrial pacing is demonstrated.

Discussion

In previous studies,[10,11] it was shown that analysis of abnormalities associated with the motion of the cardiac valves, the aortic root, the right ventricular anterior wall, the ventricular septum, and the left atrial and left ventricular walls, helped identify atrial premature beats, atrial fibrillation, atrial flutter, and AV block. The existence of cannon waves in the neck veins and their regular or irregular occurrence may also support the diagnosis of AV nodal rhythm, complete AV block, and ventricular tachycardia.[12]

Advantages of subcostal RA echocardiogram: Analysis of the subcostal RA wall echocardiogram has several advantages in the diagnosis of cardiac arrhyth-

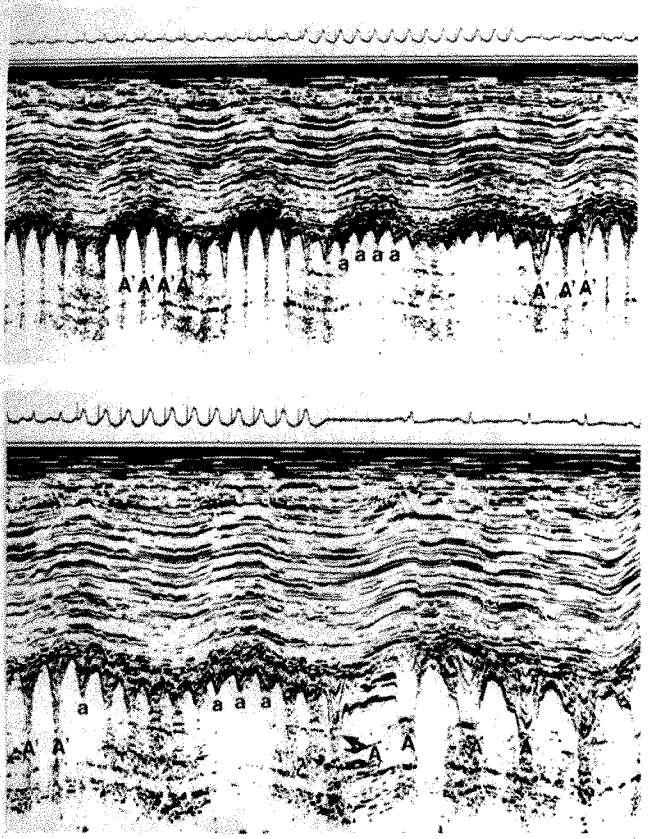

FIGURE 8. Top, subcostal RA wall echocardiogram obtained in a patient with supraventricular paroxysmal tachycardia presented by a fast rate of atrial contractions (A'). Atrial contractions (a) diminish in amplitude during ventricular overdrive pacing, when occurring during ventricular systole. After cessation of pacing, tachycardia reappears. **Bottom,** successful termination of tachycardia in the same patient. Interruption of pacing is followed by blocked atrial contraction (**arrow**) and short atrial standstill after which sinus rhythm resumes. A = normal atrial contraction.

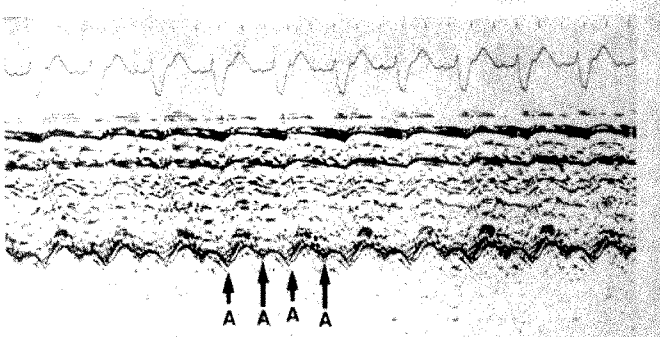

FIGURE 9. Subcostal RA wall echocardiogram of a patient with paroxysmal atrial tachycardia with block. All atrial contractions (A) are visible in the echocardiogram. Those indicated with the **long arrows** are of smaller amplitude when occurring against the closed tricuspid valve.

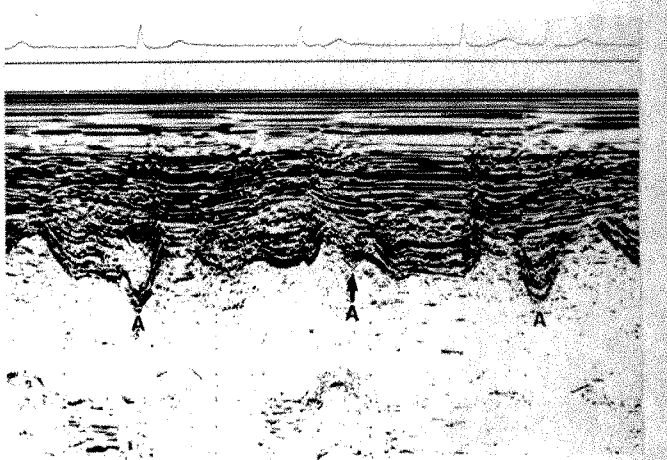

FIGURE 10. Subcostal RA wall echocardiogram in a patient with AV dissociation. The changing relation between atrial contractions (A) and QRS complexes is demonstrated. Contraction indicated by the **arrow** is aborted when occurring during ventricular systole.

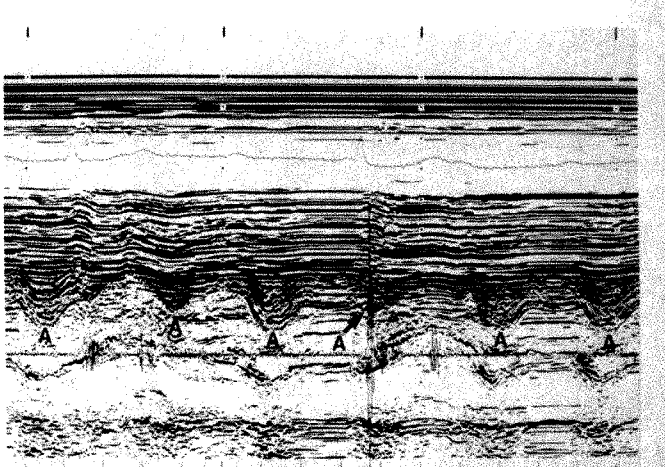

FIGURE 11. Subcostal RA wall echocardiogram of a patient with complete AV block. Atrial contractions (A) are easily recognized and are of smaller amplitude when occurring during ventricular systole (**arrow**).

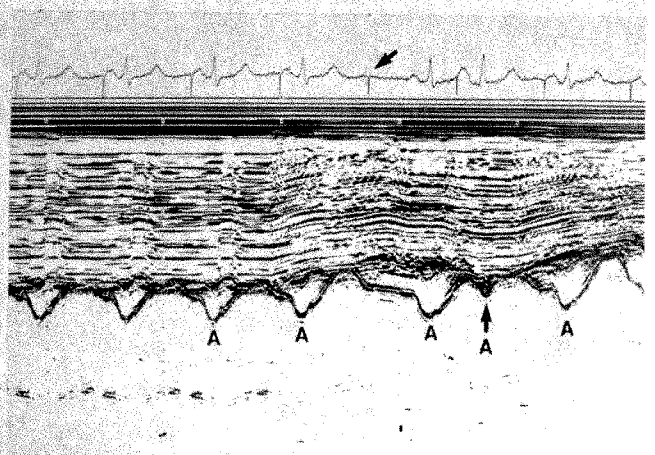

FIGURE 12. Subcostal RA wall echocardiogram obtained during temporary atrial pacing. The pacemaker spike indicated by the **arrow** did not cause atrial depolarization and is not followed by atrial contraction (A) in the echocardiogram. The sixth atrial contraction (**upward arrow**) is aborted when occurring during ventricular systole.

mias compared with the aforementioned techniques. A clear detection of atrial contraction in the subcostal RA wall echocardiogram is possible throughout the cardiac cycle during ventricular systole and diastole. The normal RA wall contraction is presented as a high amplitude posterior excursion in the subcostal echocardiogram. On the other hand, in the echocardiogram of the left atrial posterior wall, whose motion is often difficult to demonstrate, atrial systole causes only a slight anterior deflection.[13] It is of practical importance that the subcostal echocardiogram of the RA wall can be easily recorded in each person while the quality of the recording is not influenced by hyperinflation of the lungs.

This technique allows the clear detection of small voltage P waves, P waves hidden in the T waves or lost in the QRS complexes, and is superior in this respect to special chest leads and esophageal electrocardiography. The presence or absence of atrial contractions and their amplitude or timing give each arrhythmia a specific RA wall motion pattern which is helpful in their recognition with a simultaneously recorded nondiagnostic electrocardiogram.

Application to diagnosis of cardiac arrhythmias: It is therefore possible to distinguish between atrial, ventricular, and nodal premature beats and to recognize atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia, paroxysmal atrial tachycardia with block, and AV nodal tachycardia. The diagnosis of a wandering pacemaker, sinoatrial block, AV dissociation, and all degrees of AV block is facilitated. Although there was no opportunity to study patients with ventricular tachycardia, it is obvious that this technique is useful in differentiating supraventricular tachycardias with aberrant ventricular conduction from ventricular tachycardia. However, it does not help differentiate between ventricular premature beats and aberrant conduction of supraventricular impulses or between AV nodal and ventricular tachycardia, when atrial fibrillation coexists.

Subcostal RA wall echocardiographic analysis may also be of use in controlling the function of atrial pacemaker. Information regarding atrial contractility before and after institution of atrial pacing can be obtained.

Study of RA hemodynamics: Some observations of RA hemodynamics were made. In a few patients with large pericardial effusion, exaggerated RA wall motion was documented. In contrast, patients with constrictive pericarditis and some with heart failure have diminished motion amplitude with a change in the duration of various phases of the atrial cycle. We are currently investigating the association of these changes with the height of the right heart and pulmonary arterial pressures and believe that the noninvasive prediction of these pressures will be possible to some extent.

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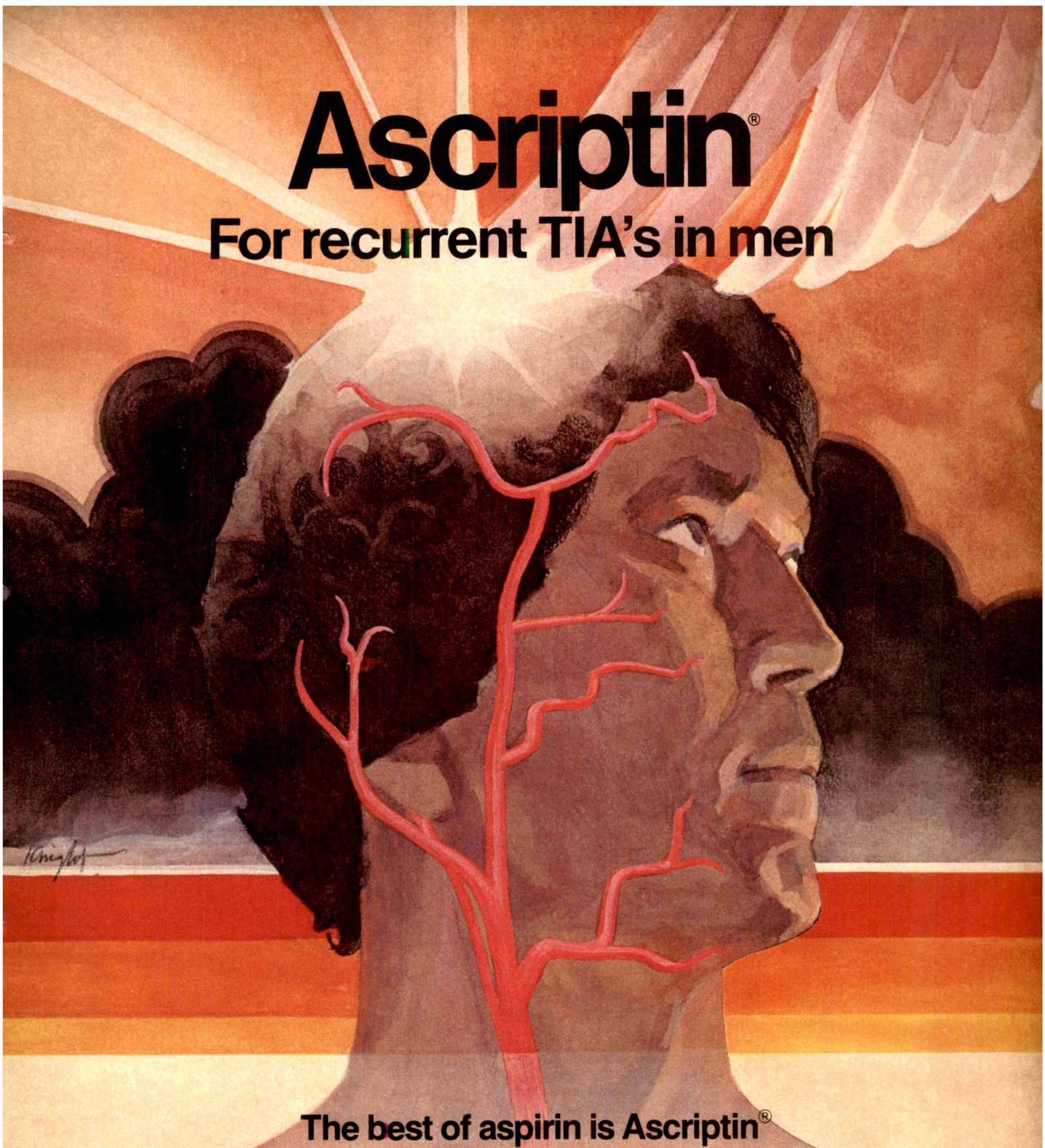

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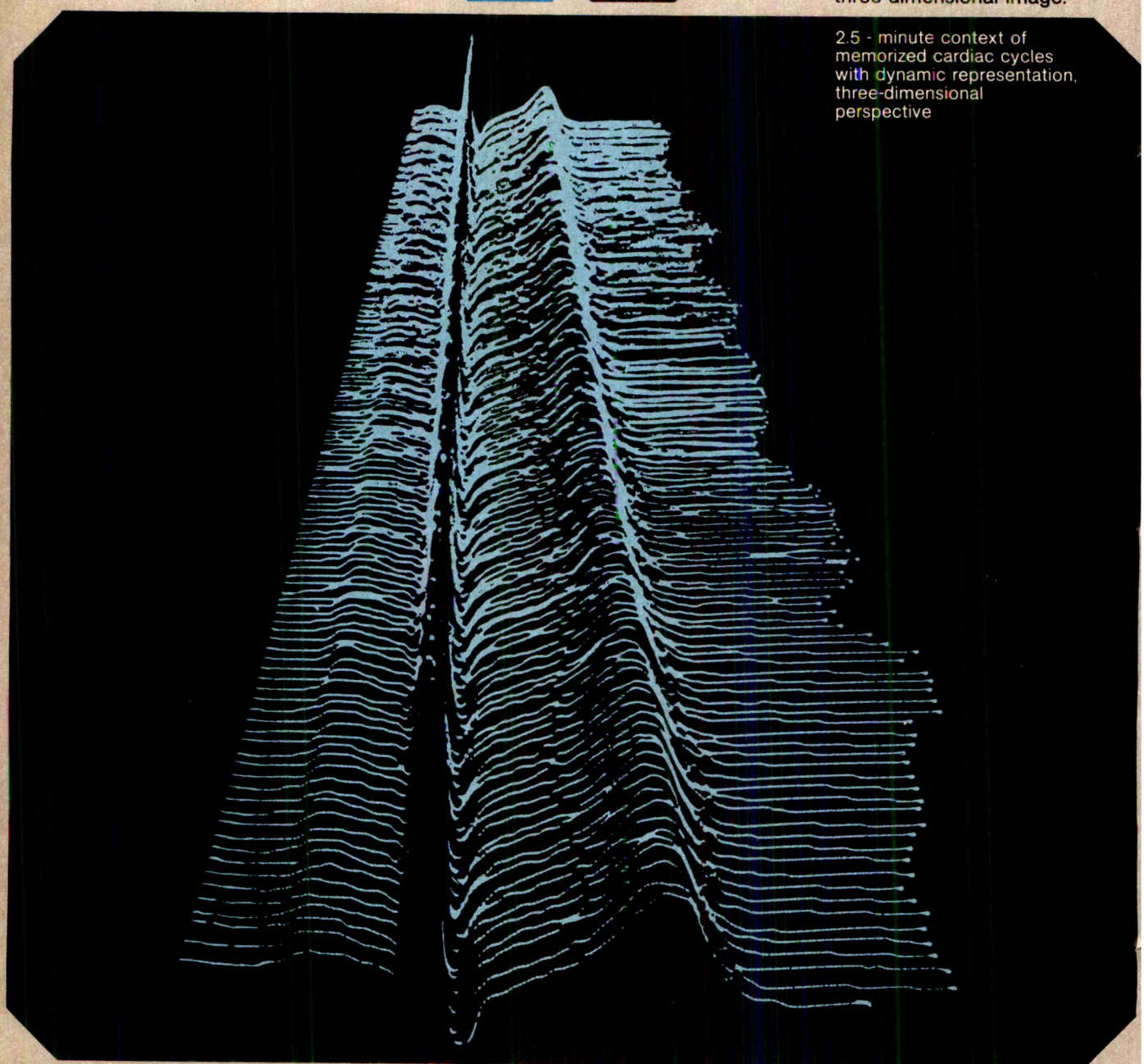

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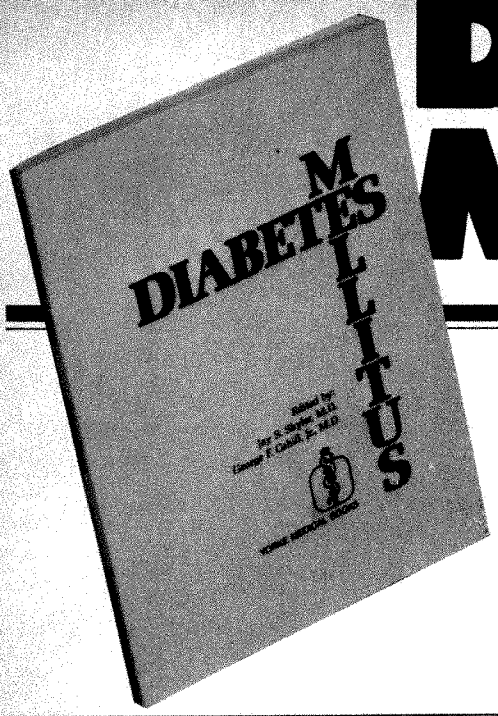

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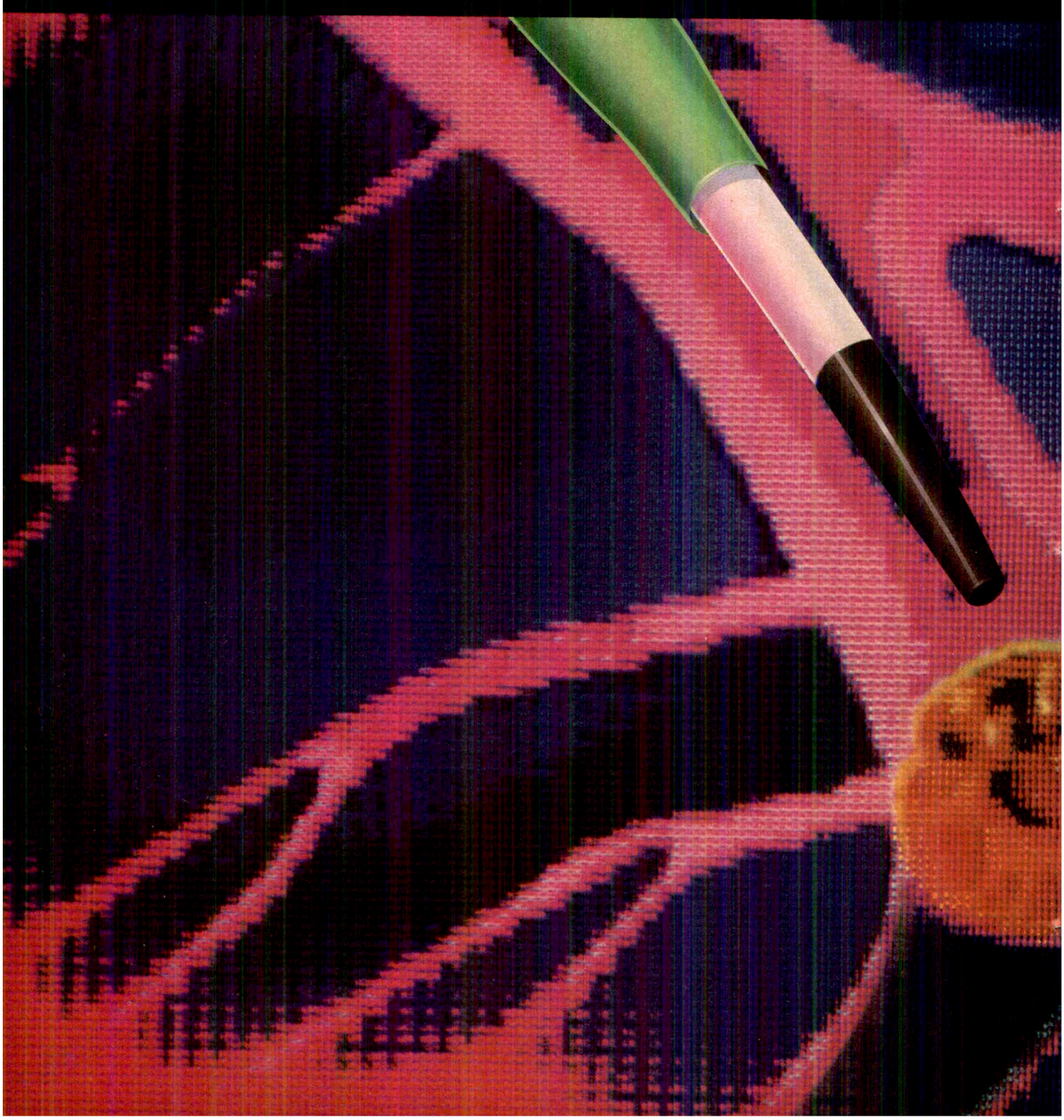

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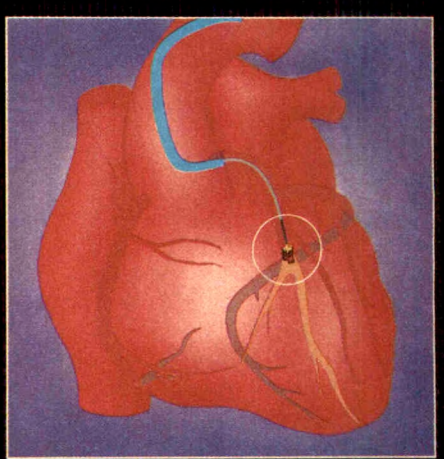

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Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

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Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion, particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram, and clinical status of patient.

ADVERSE REACTIONS
Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION
Usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

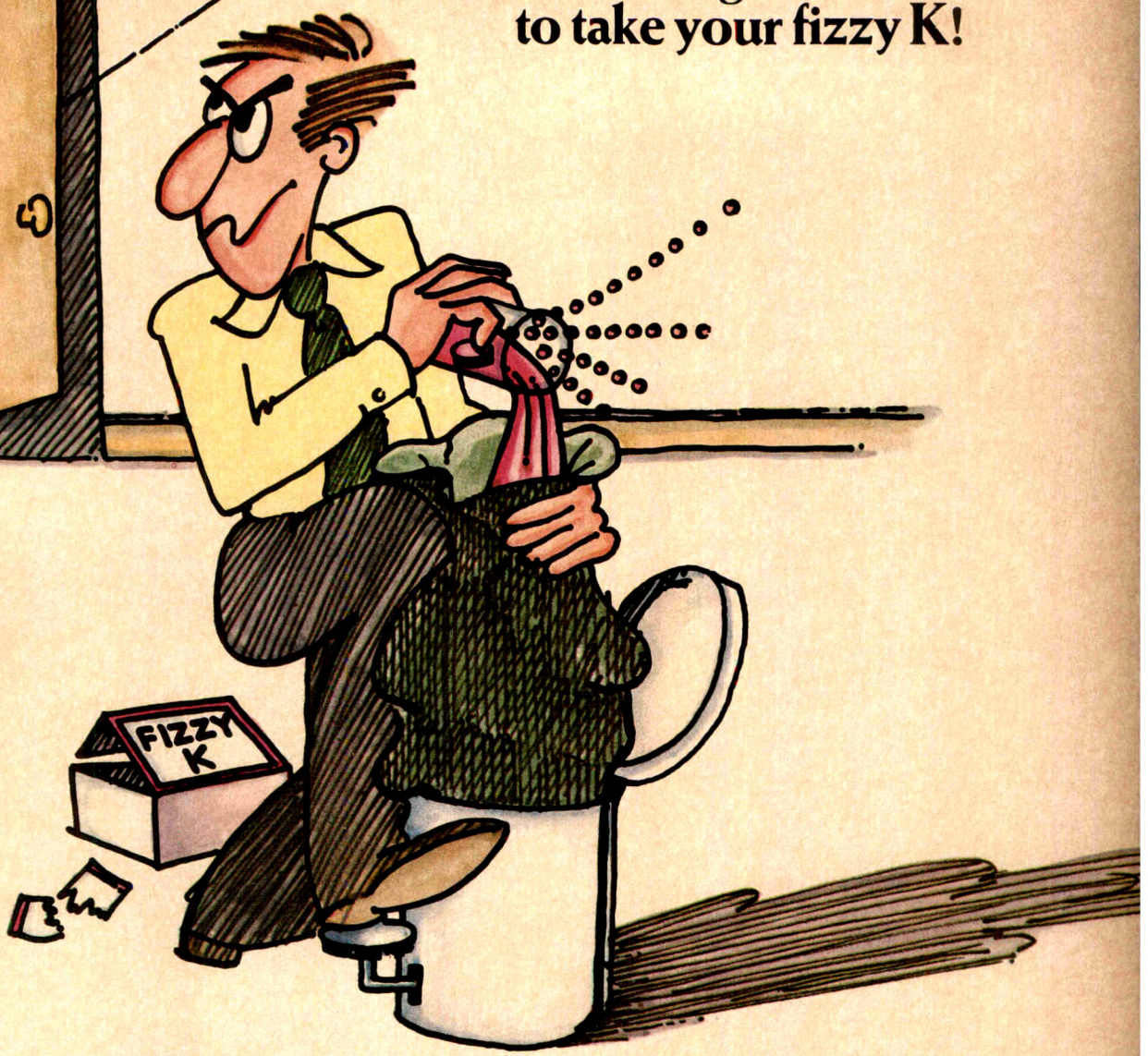
C81-72 (1/25/82)

Consult complete product literature before prescribing. 128-3678-A

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

CIBA

Take out the garbage, Ralph— and don't forget to take your fizzy K!



In correcting diuretic-induced alkalosis

the tablet that offers therapeutic substance...not fizz*

☐ Nonchloride effervescent tablets, such as K-Lyte®, and nonchloride liquids, such as Kaon® elixir, fizzle out in correcting hypochloremic alkalosis.

☐ Slow-K provides the essential chloride without the bad taste of fizzy or nonfizzy supplements.

*Slow-release potassium chloride preparations should be reserved for patients who cannot tolerate, refuse to take or have compliance problems with liquid or effervescent potassium preparations, because of reports of intestinal and gastric ulceration and bleeding with slow-release KCl preparations.

Slow-K®

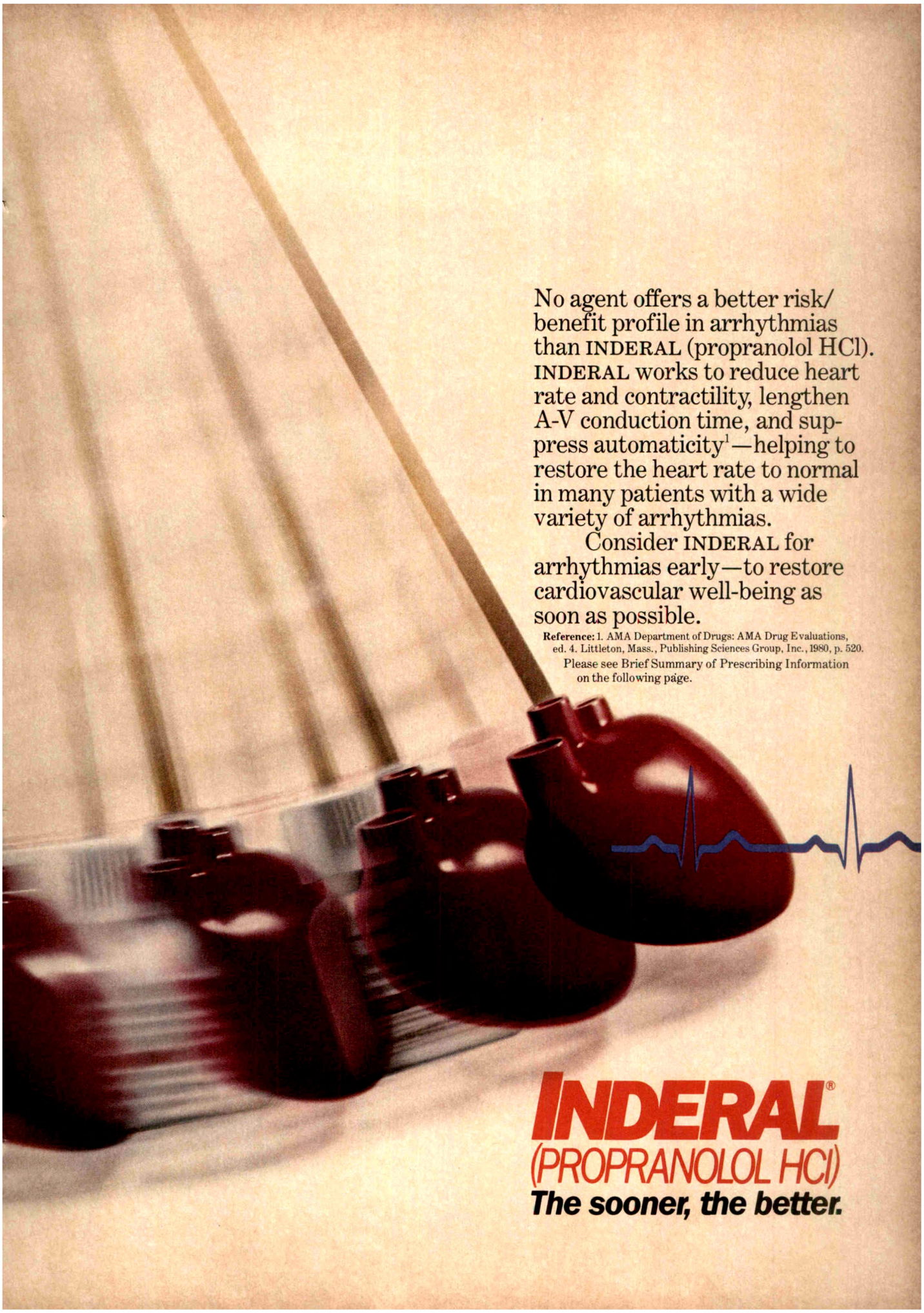
CIBA 165

potassium chloride slow-release tablets 8 mEq

Please see adjoining page for brief Prescribing Information.

CIBA

ARRHYTHMIAS
Cardiovascular well-being often begins with Inderal®
(PROPRANOLOL HCl)
Inderal®
(propranolol hydrochloride)
10 mg
100 Tablets
Ayerst
AYERST LABORATORIES INC.



No agent offers a better risk/benefit profile in arrhythmias than INDERAL (propranolol HCl). INDERAL works to reduce heart rate and contractility, lengthen A-V conduction time, and suppress automaticity[1]—helping to restore the heart rate to normal in many patients with a wide variety of arrhythmias.

Consider INDERAL for arrhythmias early—to restore cardiovascular well-being as soon as possible.

Reference: 1. AMA Department of Drugs: AMA Drug Evaluations, ed. 4. Littleton, Mass., Publishing Sciences Group, Inc., 1980, p. 520.

Please see Brief Summary of Prescribing Information on the following page.

INDERAL®
(PROPRANOLOL HCl)
The sooner, the better.

INDERAL®
(PROPRANOLOL HCl)

To restore cardiovascular well-being.

The appearance of these tablets is a trademark of Ayerst Laboratories.

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
Inderal® (propranolol hydrochloride)

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

CONTRAINDICATIONS

1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless it is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: In congestive heart failure, inhibition with beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In patients already receiving digitalis, propranolol may reduce the positive inotropic action of digitalis and may have an additive depressant effect on AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, in rare instances, cardiac failure has developed during propranolol therapy. At the first sign of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and observed closely a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Give special consideration to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol should be withdrawn slowly, since abrupt withdrawal may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta-blockade impairs the ability of the heart to respond to reflex stimuli. Except in pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery. In case of emergency surgery, the effects of propranolol can be reversed by administration of beta-receptor agonists such as isoproterenol or levarterenol, but such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), administer with caution, since propranolol may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in patients with labile diabetes. A precipitous elevation of blood pressure may accompany hypoglycemic attacks.

USE IN PREGNANCY: Safe use in human pregnancy not established. Embryotoxic effects have been seen in animals at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if propranolol is administered, since it may occasionally produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

Observe laboratory parameters at regular intervals. Use with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia, congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta-blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

HOW SUPPLIED

TABLETS

—Each hexagonal-shaped, orange, scored tablet is embossed with an "I" and imprinted with "INDERAL 10," contains 10 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0421-81) and 1,000 (NDC 0046-0421-91). Also in unit dose package of 100 (NDC 0046-0421-99).

—Each hexagonal-shaped, blue, scored tablet is embossed with an "I" and imprinted with "INDERAL 20," contains 20 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0422-81) and 1,000 (NDC 0046-0422-91). Also in unit dose package of 100 (NDC 0046-0422-99).

—Each hexagonal-shaped, green, scored tablet is embossed with an "I" and imprinted with "INDERAL 40," contains 40 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0424-81) and 1,000 (NDC 0046-0424-91). Also in unit dose package of 100 (NDC 0046-0424-99).

—Each hexagonal-shaped, yellow, scored tablet is embossed with an "I" and imprinted with "INDERAL 80," contains 80 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0428-81) and 1,000 (NDC 0046-0428-91). Also in unit dose package of 100 (NDC 0046-0428-99).

The appearance of these tablets is a trademark of Ayerst Laboratories.

Store at room temperature (approximately 25° C).

INJECTABLE

—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).

Store at room temperature (approximately 25° C)

Ayerst® AYERST LABORATORIES
NEW YORK, N.Y. 10017

8028/882

Application of Body Surface Mapping to Exercise Testing: S-T_{80} Isoarea Maps in Patients With Coronary Artery Disease

FRANK G. YANOWITZ, MD, G. MICHAEL VINCENT, MD, ROBERT L. LUX, PhD, MAHESH MERCHANT, PhD, LARRY S. GREEN, MD, and J. A. ABILDSKOV, MD

Body surface electrocardiographic maps were recorded before and after exercise in 25 men with angiographically documented coronary disease. Torso potential distributions at 192 locations were derived from a 32 lead electrode array using methods previously described in our laboratory. The S-T segment was characterized by the spatial distribution of the integral of S-T segment voltage over 80 ms (S-T_{80}). Body surface regions where the S-T_{80} areas were −8 mV·ms or greater were identified in 18 of 25 patients. The most negative S-T_{80} site on the map was called the "S-T_{80} minimum." The S-T_{80} minima were located 1 or 2 electrode rows away from the standard V_4–V_6 electrode positions in 6 of 18 patients who developed S-T_{80} areas of −8 mV·ms or greater. Our data suggest that standard electrocardiographic leads may not be optimal for identifying S-T segment depression in all patients with coronary disease. Furthermore, body surface mapping during exercise provides a more quantitative and qualitative method for characterizing the ischemic response to exercise.

The electrocardiographic response to exercise has established value for detection of ischemic heart disease.[1–7] However, it is uncertain that the usual leads employed for this purpose are optimal. Although precordial leads V_4–V_6 or a modified V_5 are most likely to show S-T segment displacement during ischemia, approximately 10% of patients with ischemia due to coronary disease have S-T segment changes only in other leads.[8] Therefore, more extensive sampling of the electrocardiogram may result in improved detection of myocardial ischemia and may also be useful in assessing the location and severity of coronary artery disease. This possibility is supported by the recent work of Fox et al.[9] employing a 16 electrode precordial grid during exercise testing. The potential for increased sensitivity and assessment of lesion location and severity makes it desirable to further evaluate more complete sampling of the body surface electrocardiogram in association with exercise testing.

Miller et al.[10] and Mirvis[11] reported results of body surface mapping with exercise in normal subjects and contributed to the development of appropriate methodology. The present study was carried out with the general objectives of further developing methodology and beginning an evaluation of clinical utility of body surface mapping during exercise testing. The specific purpose of this study was to determine whether standard precordial leads V_4–V_6 adequately sample the body surface distribution of S-T segment displacement due to ischemia.

Methods

Study patients: Twenty-five men with at least 50% luminal diameter obstruction in 1 or more coronary arteries seen angiographically were studied (Table I). Symptom-limited exercise testing was performed according to the Bruce protocol.[12] A 12 lead electrocardiogram modified for exercise testing by Mason et al.[13] and 32 lead body surface maps were obtained at rest in the supine and standing positions, immediately after exercise in the standing position and 1, 3, and 5 minutes after exercise in the supine position. The 12 lead electrocardiogram was also obtained at the end of each 3 minute stage during exercise and at maximal exercise. Each recording from the 12 and 32 lead systems was of 10 seconds' duration. Electrode

From the Department of Medicine and Division of Cardiology, LDS Hospital and the University of Utah College of Medicine, and The Nora Eccles Harrison Cardiovascular Research and Training Institute, Salt Lake City, Utah. This work was supported in part by Program Project Grant HL 13480 from the National Institutes of Health, Bethesda, Maryland, and grants from the LDS Hospital-Deseret Foundation, The Nora Eccles Treadwell Foundation, and The Richard A. and Nora Eccles Harrison Fund for Cardiovascular Research, Salt Lake City, Utah. Manuscript received December 28, 1981; revised manuscript received April 5, 1982, accepted April 16, 1982.

Address for reprints: Frank G. Yanowitz, MD, Division of Cardiology, LDS Hospital, 325 Eighth Avenue, Salt Lake City, Utah 84143.

sites were prepared with conductive paste, and after application of both lead sets, the torso was wrapped with 6 inch Ace bandages to reduce motion artifacts. All electrocardiographic comparisons were made using records obtained in the same posture. The 12 lead electrocardiographic response to exercise was interpreted by conventional visual interpretation techniques using 0.1 mV horizontal or downsloping S-T segment depression as a criterion for a "positive" test result.

Body surface map recording and measurements: The system for recording and analyzing the 32 lead body surface maps was developed in our laboratory and was previously described.[14] All 32 leads were simultaneously recorded at 1 ms intervals using signal multiplexing techniques. Each signal was amplified, digitized to 9 bits at 1,000 Hz, and stored on specially formatted flexible disks.

To obtain body surface maps, 5 to 15 P-QRS-T complexes from each of 32 leads were coherently averaged using template matching to reduce muscle noise and respiration-induced baseline shift. Baseline in the averaged complex was established by identifying a sample point in the adjacent P-R intervals at which the signal was "flat."

Torso potential distributions on a 12 × 16 grid (192 points) were estimated from potentials recorded with the 32 lead system. It has previously been demonstrated that such estimates can be made with an average error of only 35 μV RMS and an average correlation of 0.99 with respect to actual recordings from a 12 × 16 electrode grid.[14] Data were displayed as isoarea contour maps of the S-T segment. For the purpose of this study, the S-T segment was characterized as the spatial distribution of the integral of S-T segment voltage over an 80 ms interval beginning with the end of the QRS complex (J point). This "S-T_{80}" isoarea distribution represents the average S-T segment displacement for the 80 ms window. The measurement was appropriate for the purpose of the study, namely, to determine whether particular leads showed S-T segment displacement. It defines the presence of S-T segment displacement but is less sensitive to the shape of the segment than are measurements at a particular instant or a measurement of maximal displacement. Because S-T segment shape has established value in the detection of coronary artery disease, the S-T_{80} measurement is not necessarily optimal for evaluation of that disease. Definition of the most useful features of S-T segment displacement and other electrocardiographic findings in body surface maps associated with exercise testing will require studies of different design than that reported herein.

Body surface S-T_{80} isoarea maps were plotted on the format illustrated in Figure 1. The rectangle represents the thorax displayed as an unrolled cylinder. Location of the mid-axillary and mid-sternal lines is shown on the diagram. The upper margin of the rectangle represents a level just below the jugular notch and the lower margin a level just above the umbilicus. The right and left margins represent the paravertebral lines. The intersections on the grid represent 192 sites on the torso from which electrocardiographic signals are either directly measured or derived. Small dots are sites of actual electrocardiographic measurements using the 32 lead array. Three large dots indicate the locations of the standard V_4–V_6 electrodes. The numbering of rows and columns is indicated to the left of and below the grid. Dotted lines subdivide the body surface into 12 regions labeled A through L.

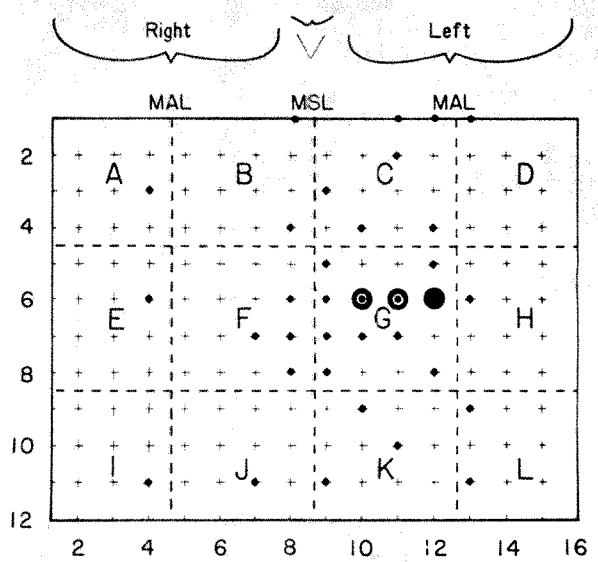


FIGURE 1. Format for plotting body surface maps. The **rows and columns** indicate the locations of 192 body surface sites from which electrocardiographic signals are either directly measured or derived. **Small dots** are the sites of actual electrocardiographic measurements. **Three large dots** indicate the location of standard V_4–V_6 electrodes. A = right upper back; B = right upper chest; C = left upper chest; D = left upper back; E = right mid-back; F = right mid-chest; G = left mid-chest; H = left mid-back; I = right lower back; J = right lower chest; K = left lower chest; L = left lower back; MAL = mid-anterior line; MSL = mid-sternal line.

Results

Clinical features of patients: Clinical, electrocardiographic, and angiographic data on the 25 patients are summarized in Table I. The mean age of these men was 55 years (±7 years standard deviation). Six patients were receiving propranolol, and 1 was on digoxin at the time of study. Twenty patients had a normal 12 lead electrocardiogram at rest, whereas 4 patients had evidence of old myocardial infarction including Q waves and ST-T wave abnormalities; 1 patient had nonspecific ST-T wave abnormalities.

With the criterion of 0.1 mV horizontal or downsloping S-T segment depression, 19 of the 25 patients (78%) had abnormal 12 lead electrocardiographic responses to exercise. Four patients had a borderline re-

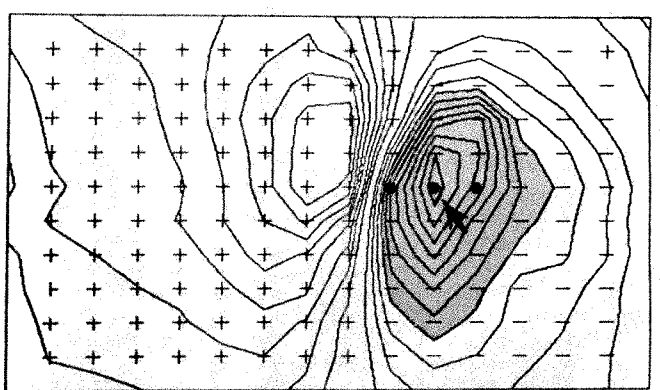


FIGURE 2. Patient 6. S-T_{80} map immediately after exercise. The **arrow** points to the location of the S-T_{80} minimum. The **shaded area** represents the ischemic zone. The **large dots** represent leads V_4–V_6.

TABLE I Clinical, Electrocardiographic, and Angiographic Results in 25 Men With Coronary Artery Disease

Case	Age (yr)	Meds	Rest ECG	Max HR	Exercise ECG	$S\text{-}T_{80}$ Minimum (mV·ms)	$S\text{-}T_{80} \geq -8$ mV·ms (%)*	$S\text{-}T_{80} \geq -8$ mV·ms Location†	CAD
1	52	...	N	130	±	−7.21	0	...	LAD
2	59	...	N	150	+	−22.34	7.7	C,*G*,H,K	RCA/LCx
3	57	...	N	88	±	−6.65	0	...	RCA/LAD
4	60	p	N	105	+	−10.74	3.6	*G*,K	RCA
5	67	...	N	100	+	−14.35	4.5	C,*G*	RCA/LM
6	57	...	N	145	+	−23.49	11.7	C,*G*,H,K	LM/LAD
7	64	...	N	137	+	−6.28	0	...	RCA/LCx
8	59	...	N	140	+	−16.49	9.1	C,*G*,K	LCx
9	43	...	N	114	±	−5.34	0	...	RCA/LAD
10	43	...	N	128	+	−14.60	7.6	C,*G*	LAD
11	48	p	AMI	140	−	−5.52	0	...	LCx
12	65	...	N	133	+	−23.22	11.2	C,*G*	RCA/LAD
13	61	...	N	149	+	−10.47	5.3	*G*,K	LAD/LCx
14	43	d	AMI	135	−	−6.71	0	...	LAD
15	61	...	N	160	+	−16.22	2.8	*G*,K	RCA
16	49	...	N	170	+	−13.12	3.6	*G*,K	RCA/LAD
17	62	...	IMI	113	±	−7.90	0	...	RCA/LAD/LCx
18	51	p	N	120	+	−22.13	14.1	C,*G*,H,K	RCA/LAD/LCx
19	55	...	N	130	+	−24.74	30.2	C,D,*G*,H,K,L	RCA/LCx
20	55	p	N	108	+	−16.99	6.3	C,*G*	LM/LCx
21	64	p	N	110	+	−25.90	17.4	C,*G*,H,K,L	RCA/LM/LAD/LCx
22	57	...	IMI	140	+	−15.80	2.8	*G*	RCA/LCx
23	59	...	STT	135	+	−15.11	4.0	*G*	LAD
24	43	p	N	120	+	−18.86	11.6	C,D,*G*,H,K	RCA/IAD
25	52	...	N	125	+	−20.85	14.7	C,D,*G*,H,K	LAD

* Percentage of total body surface map occupied by this negative area.
† Italicized letter indicates the $S\text{-}T_{80}$ minimum location on the surface map.
AMI = anterior infarct pattern; C = left upper chest; CAD = coronary artery disease; d = digoxin; D = left upper back; ECG = electrocardiogram; G = left mid-chest; H = left mid-back; HR = heart rate; IMI = inferior infarct pattern; K = left lower chest; L = left lower back; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LM = left main coronary artery; Meds = medications; N = normal resting electrocardiogram; p = propranolol; RCA = right coronary artery; STT = ST-T wave changes; + = abnormal electrocardiographic response to exercise; − = normal electrocardiographic response to exercise; ± = borderline electrocardiographic response to exercise (0.05–0.1 mV S-T segment depression).

sponse (0.05 to 0.1 mV S-T segment depression), and 2 patients had a normal exercise test. These results are comparable to previously published data on the sensitivity of exercise testing in patients with documented coronary artery disease.

Analysis of $S\text{-}T_{80}$ isoarea maps (Table I): The effects of exercise on the body surface distribution of $S\text{-}T_{80}$ isoarea contours will not be characterized as normal or abnormal because criteria for such classification have not been established. The following descriptors of the $S\text{-}T_{80}$ maps were analyzed to better define the distribution of S-T segment displacement due to myocardial ischemia: (1) the body surface location of the most negative $S\text{-}T_{80}$ area for each patient (defined as the $S\text{-}T_{80}$ minimum); (2) the magnitude of the $S\text{-}T_{80}$ minimum; (3) the size and location of the body surface region(s) represented by $S\text{-}T_{80}$ areas of −8 mV·ms or greater (more negative). This last variable represents the body surface distribution of sites where Wilson terminal electrocardiographic leads would record an average of 0.1 mV or greater S-T segment depression over an 80 ms period.

Eighteen of the 25 patients (72%) developed $S\text{-}T_{80}$ minima more negative than −8 mV·ms and therefore developed zones of S-T segment depression of more than 0.1 mV averaged over 80 ms. These regions of S-T segment depression included the left mid-anterior thorax in all 18 patients. In 9 of them, the $S\text{-}T_{80}$ minimum was located at the conventional V_5 electrode position, and in 3 patients the $S\text{-}T_{80}$ minimum was in close proximity to the V_4 electrode position. In the remaining 6 patients, the $S\text{-}T_{80}$ minimum occurred at body sites other than the standard V_4–V_6 electrode positions. Five of the 6 had $S\text{-}T_{80}$ minima located 1 or more electrode rows inferior to the V_4–V_6 electrode sites; in 1 patient the minimum S-T segment displacement was located 1 electrode row superior to the V_5 chest position. In 5 of the 6 patients, the $S\text{-}T_{80}$ area of −8.00 mV·ms or greater included 1 or more of the V_4–V_6 sites although these sites did not sample the peaks of the distribution.

Of the 7 patients in whom $S\text{-}T_{80}$ minima of −8 mV·ms or greater did not develop, 3 had previous myocardial infarction and were not complaining of angina pectoris at the time of study. The resting $S\text{-}T_{80}$ maps in these 3 patients showed regions of positive $S\text{-}T_{80}$ isoarea contours coinciding with S-T segment elevation on the individual electrocardiographic signals. Too few patients were studied to correlate regions of positive $S\text{-}T_{80}$ areas with angiographic data or location of infarction.

Representative cases: Several examples of patients in whom $S\text{-}T_{80}$ areas of −8.00 mV·ms or greater developed are illustrated in Figures 2 to 4. Figure 2 shows the $S\text{-}T_{80}$ map from the immediate recovery period in Patient 6. The shaded area represents the zone of S-T segment depression averaging at least 0.1 mV or greater. The $S\text{-}T_{80}$ minimum, indicated by

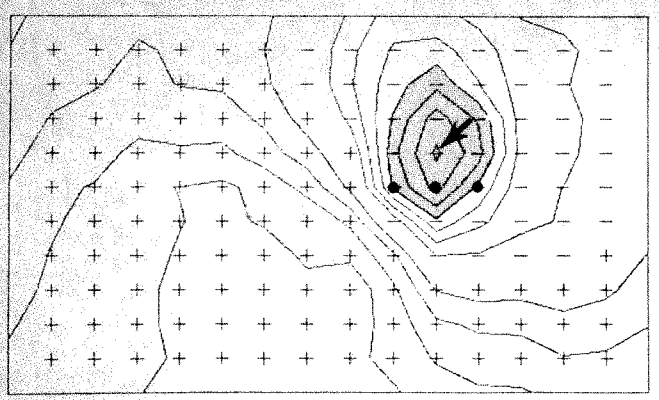


FIGURE 3. Patient 5. S-T_{80} map immediately after exercise. The **arrow** points to the location of the S-T_{80} minimum. The **shaded area** represents the ischemic zone.

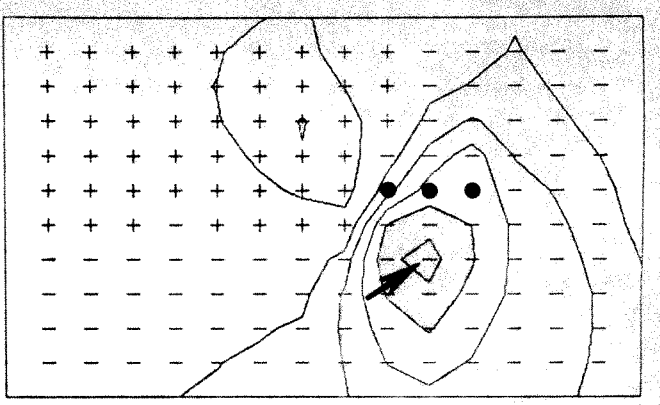


FIGURE 4. Patient 4. S-T_{80} map 1 minute after exercise. The **arrow** indicates the S-T_{80} minimum. The **shaded area** represents the ischemic zone.

the arrow, was −23.49 mV·ms and was located at the standard V_5 electrode site. Coronary angiography revealed an 80% left main coronary stenosis and a 75% stenosis of the 1st diagonal branch.

Figure 3 illustrates the S-T_{80} map of Patient 5. The shaded area again locates the regions on the map where S-T segment depression averaged 0.1 mV or greater. In this patient with a 70% left main coronary stenosis and 75% obstruction of the mid-right coronary artery, the S-T_{80} minimum was located superior to the V_5 chest position (arrow).

In Figure 4 the S-T_{80} map from Patient 4 shows a small shaded zone inferior to the V_4–V_6 chest positions where S-T segment depression averaged 0.1 mV or greater. During this period (1 minute after exercise), the standard electrocardiographic leads did not show significant S-T segment depression. Coronary angiography revealed complete occlusion of the right coronary artery and 50% stenosis of the left anterior descending artery.

Correlation with coronary angiography: The possible relations of coronary artery disease location and severity to body surface distributions of S-T_{80} areas were investigated. In this small group of patients, there was no significant difference in the magnitude of the S-T_{80} minimum or apparent difference in the extent of S-T_{80} negative areas in patients with single as compared with multiple vessel disease. In patients with single vessel disease, there was suggestive but not conclusive evidence that the body surface distribution of S-T segment depression was related to the diseased vessel. Patients with isolated right or left circumflex coronary artery lesions (Cases 4, 8, and 15) had negative S-T_{80} areas in the left lower part of the chest (region K). The location of the S-T_{80} minimum was 2 electrode rows inferior to the V_5 electrode site in 2 of these patients (Cases 4 and 8). In the 3 patients with isolated left anterior descending coronary disease who had S-T_{80} areas more negative than 0.8 mV·ms (Cases 10, 23, and 25), the S-T_{80} minimum was located on the V_5 chest position in all 3 patients.

Discussion

A variety of electrocardiographic lead systems have been evaluated in the exercise laboratory in an attempt to find an optimal set for quantitating the ischemic response to exercise in patients with coronary artery disease. The regional and localized nature of myocardial ischemia precludes any simple lead arrangement that is ideal for all patients. The classic study of Blackburn et al.[8] concluded that the most sensitive single electrode position was the V_5 chest location. Nevertheless, in approximately 10% of their patients the ischemic response was confined to leads with an infero-superior orientation. Most exercise laboratories now use multiple leads to maximize the probability of detecting ischemic electrocardiographic abnormalities in all patients with significant coronary artery disease.

In addition to diagnosing the presence or absence of myocardial ischemia in patients undergoing exercise testing, an ideal electrocardiographic lead system should enable a more quantitative description of the size and location of ischemic myocardial lesions. This information would likely have important clinical implications in patients undergoing exercise evaluations.

Considerable evidence that electrocardiographic examination can be improved by extensive lead sampling has been reported. Clinical studies provide evidence of improved recognition of right ventricular hypertrophy,[15] cardiomyopathy,[16] myocardial infarction,[17] and the location of anomalous atrioventricular conduction pathways.[18] The application of mapping techniques to exercise testing was only recently investigated. The published reports are mainly concerned with methodologic considerations and focus primarily on normal subjects.[10,11]

Role of exercise testing using body surface mapping: Our study suggests that potentially useful electrocardiographic information may be obtained from patients with coronary artery disease during exercise testing using body surface mapping. Of patients with independently documented coronary disease 25% had maximal depression of S-T segment area at sites other than those usually employed in exercise testing. Even though S-T segment area depression was present at the usual sampling sites in most of these patients, the finding that these sites did not sample the maximal depression suggests that improved sensitivity of exercise testing for coronary disease may be possible using body

surface mapping. These findings are compatible with those of Fox et al.[9] in which 13 patients with angiographically proved coronary disease and normal 12 lead exercise tests had S-T segment depression associated with exercise at some sites on a 16 lead precordial grid.

Our study was not extensive enough to adequately evaluate the possibility that body surface mapping may be useful in differentiating the site or defining the severity of coronary artery disease. Some suggestive evidence concerning disease site was obtained, however. All patients with isolated right coronary or left circumflex coronary artery disease had $S\text{-}T_{80}$ minima located on the left lower part of the chest. The study included only 3 patients with an isolated left anterior descending coronary lesion, but in 2 of these the $S\text{-}T_{80}$ minima were not located on the left lower chest. No significant difference was found between patients with single and those with multivessel disease in the magnitude of maximal $S\text{-}T_{80}$ depression or size of the $S\text{-}T_{80}$ area depression of more than 8 mV·ms. However, the possibilities of predicting both location and severity of coronary artery disease by means of body surface mapping should be further evaluated with large numbers of patients and with electrocardiographic variables in addition to the $S\text{-}T_{80}$ area employed in this study.

The S-T segment displacement averaged over 80 ms as measured in this study is not necessarily or even likely to be the most useful electrocardiographic marker of myocardial ischemia. It was considered appropriate for the purpose of this study, which was to determine whether body surface mapping furnished information about the presence and degree of S-T segment displacement that was not evident in the 12 lead examination. Definition of optimal measurements of body surface maps for the detection as well as possible definition of site and severity of coronary artery disease will require additional studies. Such optimal variables will likely include S-T segment slope and magnitude at 80 ms after the J-point.

Conclusion: Body surface mapping after exercise showed that maximal depression of the S-T segment occurred at sites not usually sampled in one fourth of patients with arteriographically proved coronary artery disease. This finding suggests that increased sensitivity of exercise testing may be possible with body surface mapping. Suggestive evidence that body surface mapping may be helpful in defining the location of single vessel disease was also obtained. This possibility and that of estimating the severity of coronary artery disease by body surface mapping with exercise needs further study with larger numbers of patients and electrocardiographic measurements in addition to the one employed in this study.

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Scintigraphic Prediction of Pulmonary Arterial Systolic Pressure by Regional Right Ventricular Ejection Fraction During the Second Half of Systole

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In 49 patients in whom gated equilibrium ventriculography and cardiac catheterization were performed within a 6 day interval, total and fractional portions of global and regional right ventricular ejection fraction (RVEF) were correlated with pulmonary arterial systolic pressure. Pulmonary arterial systolic pressure was normal (30 mm Hg or less) in 27 patients (Group I) and elevated (31 mm Hg or greater) in 22 patients (Group II). The second-half regional RVEF was 38 ± 8% (mean ± standard deviation) with a range of 30 to 54% for Group I and 22 ± 6% with a range of 13 to 32% for Group II. The difference between the means was statistically significant ($p < 0.001$). Use of a second-half regional RVEF of 30% as the criterion of elevated pulmonary arterial systolic pressure resulted in a sensitivity of 0.86 and a specificity of 1.00. A power curve fit in which pulmonary arterial systolic pressure = 10.91 (second-half regional RVEF)$^{-0.87}$ allowed accurate estimation ($r = -0.85$) of pulmonary arterial systolic pressure from the second-half regional RVEF. It is concluded that second-half regional RVEF may be used to accurately detect pulmonary arterial hypertension and to estimate its extent.

Gated equilibrium ventriculography provides a noninvasive technique for the evaluation of both left and right ventricular (RV) function and wall motion.[1-6] Several investigators[3,6] have used regional changes in count rate to assess quantitatively regional left ventricular (LV) wall motion. In this study we used this approach to assess quantitatively regional (free wall) RV wall motion. The free wall is of special interest because the major contractile motion involved in RV systolic performance is the inward motion of the free wall toward the interventricular septum.[7] We compared various portions of regional and global RV ejection with pulmonary arterial systolic, diastolic and mean pressures, RV systolic pressure, and pulmonary vascular resistance.

Methods

Patient group: The study group consisted of 49 patients from the Brigham and Women's Hospital who had undergone gated equilibrium ventriculography and cardiac catheterization performed within 6 days of each other (1.8 ± 1.6 days, mean ± standard deviation [SD]). Twenty-nine patients who had undergone both studies within 6 days were excluded because of atrial fibrillation (n = 11), clinically evident tricuspid regurgitation (n = 4), and discontinuities in the RV free wall (n = 14). The RV wall was identified from the ejection fraction image.[8] Discontinuities in the RV free wall were defined as regions with an ejection fraction less than 50% occurring within the RV free wall region of interest and involving the full thickness of the free wall. Reasons for discontinuities in the RV free wall included old RV infarction and technical factors such as right atrial interference due to incomplete separation of the right atrium and right ventricle.

There were 35 men and 14 women whose average age was 54 years (range 20 to 78). Their clinical diagnoses are listed in Table I. A majority of the patients had coronary heart disease defined on cardiac catheterization as greater than 50% luminal narrowing of at least 1 major coronary arterial branch. Five patients had previous cardiac surgery including coronary

TABLE I Distribution of Diagnoses in Group I (Pulmonary Arterial Systolic Pressure 30 mm Hg or Less) and Group II (Pulmonary Arterial Systolic Pressure Greater Than 30 mm Hg)

Diagnosis	Patients (n)	Group I	Group II
Coronary artery disease	23	15	8
Aortic valve disease	10	4	6
Mitral valve disease	8	2	6
Atypical chest pain (normal coronary arteries)	5	5	0
Atrial septal defect	6	3(3)*	3(2)*
Cardiomyopathy	2	0	2
Chronic pulmonary disease	1	0	1
Ventricular septal defect	1	0	1(1)*

* The numbers in parentheses represent the patients with right ventricular volume overload.

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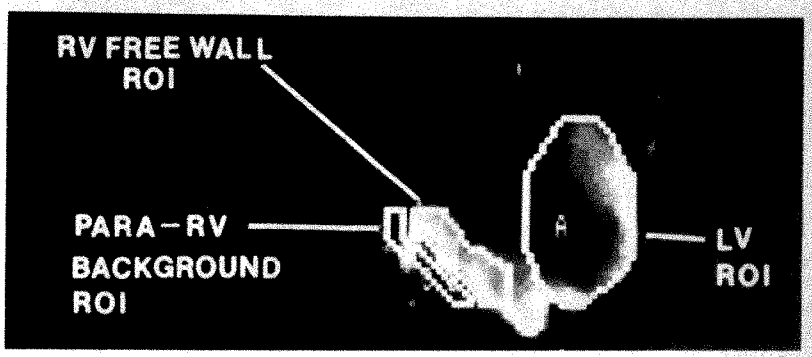

FIGURE 1. Ejection fraction image in modified left anterior oblique projection with left ventricular, right ventricular, and para-right ventricular (Para-RV) background regions of interest (ROI).

arterial bypass grafting in 2 patients, and repair of an atrial septal defect, aortic valve replacement, and mitral valve replacement in 1 patient each.

Cardiac catheterization: Each patient underwent right and retrograde left heart catheterization, including left ventriculography, and 40 patients had coronary arteriography. Patients were premedicated with diazepam, 5 to 10 mg orally, and diphenhydramine, 25 to 50 mg orally. With the patient supine and in the resting state, systemic arterial, LV, pulmonary capillary wedge, pulmonary arterial, RV, and right atrial pressures were measured using fluid-filled catheters which were calibrated with the mid-chest as the baseline. Pulmonary and systemic blood flows and resistances were calculated by the Fick principle on the basis of measured oxygen consumption. In 1 patient with an atrial septal defect and 1 patient with chronic pulmonary disease, pulmonary arterial pressures were obtained before and after the inhalation of oxygen.

The patients were classified into 2 groups. Twenty-seven patients (Group I) had normal pulmonary arterial systolic pressure (30 mm Hg or less) and 22 patients (Group II) had elevated pulmonary arterial systolic pressure (greater than 30 mm Hg).

Radionuclide data acquisition: In vivo red blood cell labeling was performed by the intravenous injection of 5 mg of unlabeled stannous pyrophosphate (Pyrolite, New England Nuclear) followed in 15 to 20 minutes by approximately 25 mCi of technetium-99m pertechnetate.[9] The studies were obtained with a portable Anger scintillation camera with a high sensitivity, 30° slant hole collimator (Engineering Dynamics, Lowell, Massachusetts), as previously described.[8,10] The patient was positioned in the modified left anterior oblique position with the long axis of the left ventricle aligned vertically, and the obliquity adjusted to provide the greatest separation of the right and left ventricles.[3,8] The use of this position has been validated for global RVEF; left or right atrial interference was minimized because of the 30° caudal tilt.[11]

After equilibration of the radionuclide in the intravascular space (about 5 to 10 minutes), gated (25 ms) images were collected and stored in frame mode on a digital computer (PDP 11/34, Digital Equipment). Only cycles within a cardiac cycle length tolerance of ±50 ms were processed.

The 2 patients who had pulmonary arterial pressure measured with and without oxygen also had gated equilibrium studies performed before and during the inhalation of oxygen.

Data processing: Global and regional LV function were assessed quantitatively and an ejection fraction image was obtained by methods previously described.[8] With use of the ejection fraction image, a region-of-interest was placed around the RV free wall, including all pixels greater in intensity than the mid-point of a 16-shade value scale and thus greater than 50% of corrected end-diastolic counts, avoiding the right atrium and including the apex of the right ventricle (Fig. 1). The medial border of the RV free wall region-of-interest in the apical region was extended to within 1 to 3 pixels of a line extended downward from the most medial point of the septal portion of the LV region-of-interest. A para-RV background region-of-interest 1 to 2 pixels lateral to the outer border of the RV free wall region-of-interest and 3 to 4 pixels in width, extending the full length of the free wall region-of-interest, was also drawn (Fig. 1).

The RV free wall region-of-interest time-activity curve was then printed. The RV end-diastolic frame (50 ms frame with the largest number of counts just before ejection), end-systolic frame (50 ms frame with the lowest number of counts at the end of ejection), mid-systolic, one-third systolic and two-thirds systolic frame (50 ms frame at one half, one third, and two thirds of RV systole) were selected. To improve the statistical reliability of the data, each 50 ms frame was derived by adding 2 adjacent 25 ms images. Background correction was made by dividing the number of counts in the para-RV background region-of-interest at end-diastole (50 ms frame) by the number of pixels in the para-RV background region-of-interest, thus normalizing the background per pixel. The product of the para-RV background per pixel and the number of pixels in the RV free wall region-of-interest were subtracted from the RV free wall region-of-interest end-diastolic counts to obtain the background-corrected end-diastolic counts.

The second half, last third, and total regional RVEF were defined by subtracting the counts in the end-systolic frame from the counts in the mid-systolic, two-thirds systolic, and end-diastolic frames, respectively, and dividing the differences by the background-corrected end-diastolic counts. The middle-third regional RVEF was defined by subtracting the counts in the one-third systolic frame from counts in the two-thirds systolic frame and dividing the difference by the background-corrected end-diastolic counts.

Global RVEF was determined in representative patients, 22 from Group I and 15 from Group II, using a computer-selected background and a single region-of-interest excluding the infundibulum. The second-half global RVEF was also determined in 9 representative patients from Group I and 9 patients from Group II with the same regions-of-interest used for calculating global RVEF. The second-half global RVEF was defined in the same manner as the second- half regional RVEF except that global- and computer-selected background regions-of-interest were substituted for the RV free wall and para-RV background regions-of-interest.

Reproducibility was evaluated in 7 patients who had undergone repeated gated equilibrium studies several hours apart. Studies were performed after repositioning both the patient and the scintillation camera but without significant change in the patient's clinical status. In each case, the left,

TABLE II Comparison of Fractional and Total, Regional, and Global RVEF in Groups I and II

	Group I (n = 27) (PASP 24.7 ± 3)	Group II (n = 22) (PASP 46.2 ± 13)	2-Sample *t* Test
Regional			
Second half (%)	38 ± 8	22 ± 6	p <0.001
Last third (%)	14 ± 4	7 ± 3	p <0.001
Total (%)	81 ± 16	61 ± 14	p <0.001
Global	(PASP 25.1 ± 3)	(PASP 45.5 ± 12)	
Second half %	24 ± 6	28 ± 9	NS
	(PASP 24.8 ± 3)	(PASP 45.0 ± 11)	
Total (%)	49 ± 7	44 ± 13	NS

* PASP = Mean pulmonary arterial systolic pressure ± SD (mm Hg). The mean PASP ± SD for each of the representative subgroups of Groups I and II used in the comparison of global RVEF is shown above their respective ejection fractions.

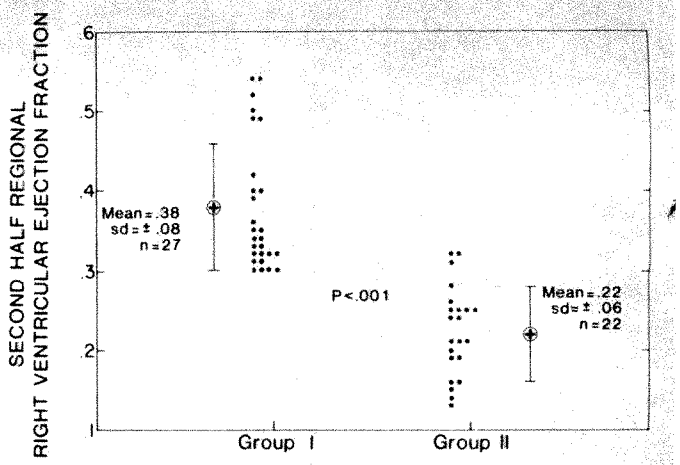

FIGURE 2. Comparison of second-half regional RVEF in patients with normal (30 mm Hg or less, Group I) and elevated (greater than 30 mm Hg, Group II) pulmonary arterial (PA) systolic pressure. Note that the second-half RVEF was significantly lower in the patients with elevated pulmonary arterial systolic pressure.

right, and background regions-of-interest were drawn independently.

To determine the interobserver error, 10 studies were randomly selected and analyzed independently by 2 observers. To determine the intraobserver variability, 10 studies were analyzed by 1 observer on separate occasions at least 6 months apart.

Radionuclide-hemodynamic comparison: To determine the utility of the various radionuclide methods in detecting patients with abnormal pulmonary arterial systolic pressure, a modified 2-sample *t* test was used to compare Groups I and II. Any p value less than 0.05 was considered significant. After examination of the data, the correlation between pulmonary arterial systolic pressure and global as well as regional RVEF was assessed using linear, logarithmic, and power fits. The correlation between second-half regional RVEF and pulmonary arterial diastolic and mean pressures, RV systolic pressure, and pulmonary vascular resistance was also assessed with linear, logarithmic, and power fits.

Results

Second-half regional RVEF: The second-half regional RVEF for Group I (normal pulmonary arterial pressure) was 38 ± 8% (mean ± SD), with a range of 30 to 54%. The second-half regional RVEF for Group II (elevated pulmonary arterial pressure) was 22 ± 6%, with a range of 13 to 32%. The difference between the means was statistically significant (p <0.001). When we used a second-half regional RVEF less than 30% as the criterion of elevated pulmonary arterial systolic pressure, the result was a sensitivity of 0.86 and a specificity of 1.0 for separation of patients with normal and elevated pulmonary arterial systolic pressure.

There was no significant difference between Groups I and II when total or second-half global RVEF was used (Table II). However, there were significant differences between the 2 groups when regional RVEF was used. The use of second-half regional RVEF resulted in the best separation of the 2 groups (Fig. 2).

Predicting elevated pulmonary arterial pressure from second-half regional ejection fraction: Preliminary examination of data showed a nonlinear relation of second-half regional RVEF and pulmonary arterial systolic pressure. A power curve fit with a pulmonary arterial systolic pressure of 10.91 (second-half regional RVEF)$^{-0.87}$ allowed estimation of pulmonary arterial systolic pressure ($r = -0.85$) (Fig. 3). The logarithmic fit also appeared to accurately predict pulmonary arterial systolic pressure ($r = -0.84$). There was some clustering of points in the 20 to 28% range of second-half regional RVEF with pulmonary arterial sys-

TABLE III Correlation Using Linear, Logarithmic, and Power Fits of Pulmonary Arterial Systolic Pressure With Fractional and Total, Regional, and Global RVEF

	Type of Fit		
	Linear	Logarithmic	Power
Regional			
Second half	−0.76	−0.84	−0.85
Last third	−0.65	−0.71	−0.71
Middle third	−0.50	−0.40	−0.35
Total	−0.56	−0.52	−0.57
Global			
Second half	−0.31	−0.38	−0.30
Total	−0.42	−0.49	−0.43

TABLE IV Comparison of Second-Half Regional RVEF with Pulmonary Mean Pressure, Pulmonary Diastolic Pressure, Right Ventricular Systolic Pressure, and Pulmonary Vascular Resistance

	Type of Fit		
	Linear	Logarithmic	Power
Pulmonary arterial mean pressure	−0.76	−0.81	−0.72
Pulmonary arterial diastolic pressure	−0.73	−0.79	−0.78
RV systolic pressure	−0.73	−0.74	−0.81
Pulmonary vascular resistance	−0.44	−0.44	−0.47

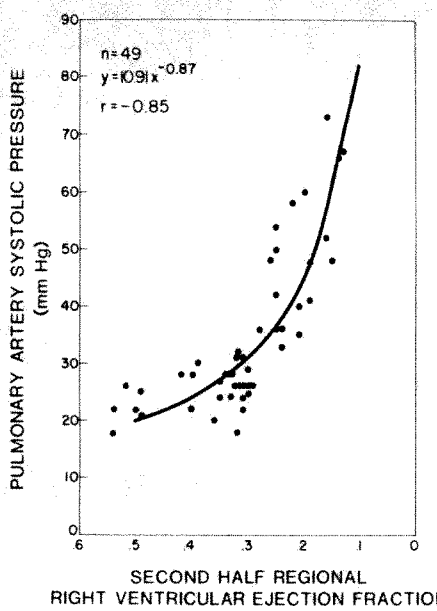

FIGURE 3. Correlation between pulmonary arterial systolic pressure and second-half RVEF.

tolic pressure of 32 to 60 mm Hg. Correlations of pulmonary arterial systolic pressure with total global, second-half global, total regional, second-half regional, middle-third regional, and last-third regional RVEF are shown in Table III. The correlation of second-half regional RVEF with pulmonary mean pressure, pulmonary arterial diastolic pressure, RV systolic pressure, and pulmonary vascular resistance are shown in Table IV. The best correlation obtained was between second-half regional RVEF and pulmonary arterial systolic pressure.

Effect of oxygen therapy: Two patients treated with oxygen both demonstrated a decrease in pulmonary arterial systolic pressure and an increase in second-half regional RVEF during oxygen therapy (Table V). Although the directional change in second-half regional RVEF was appropriate, the change was greater than would be expected from the decrease in pulmonary arterial systolic pressure alone after inhalation of oxygen during cardiac catheterization.

Reproducibility: The intra- and interobserver errors were low. Correlation between the second-half regional RVEF obtained by the same observer was good (r = 0.85), with a standard error of the estimate of the second measurement given the first of 0.06. The absolute mean difference between the 2 measurements was 0.01. Correlation between the 2 observers was good (r = 0.77), with a standard error of the estimate of 0.08. The absolute mean difference between the 2 observers was 0.04.

Correlation was also good between the results of the first and second run in patients having 2 independent studies (r = 0.77). The standard error of the estimate of the second measurement given the first was 0.04, and the absolute mean difference between the 2 measurements was 0.01.

TABLE V Summary of Studies in Patients Before and After the Inhalation of Oxygen*

	Patient 1		Patient 2	
	Off Oxygen	On Oxygen	Off Oxygen	On Oxygen
Pulmonary arterial systolic pressure (mm Hg)	60	46	63	58
Pulmonary vascular resistance (dynes-s-cm^{-5})	394	. . .	509	426
Second-half regional RVEF (%)	20	42	22	33
Global RVEF (%)	48	45	33	32

* Patient 1 had chronic obstructive lung disease and was studied before and during the administration of 32% oxygen; Patient 2 had an atrial septal defect and was studied before and during the administration of 100% oxygen.

Discussion

Use of regional RV function: The complex geometric shape of the right ventricle has been a major impediment to the study of RV volume and function. Assessment of global RV function from gated equilibrium studies has been hindered by activity emanating from adjacent structures such as the right atrium and left ventricle. The modified left anterior oblique view[10] provides an opportunity to isolate the free wall of the right ventricle and to study the ejection of blood resulting from the movement of the free wall toward the septum without right atrial or left ventricular interference.

Although the importance of the RV free wall has been questioned,[12–14] recent studies suggest that it is especially important in RV contraction[7,15–17] and have shown its increased prominence in patients with pulmonary hypertension.[18–21] Rushmer[7] postulated that the geometric configuration of the right ventricle is very important in the afterload dependence of this chamber. The right ventricle surface area is large in comparison with its volume. Normally the right ventricle ejects blood by a uniform reduction in the RV free wall-to-septal distance and in its free wall surface area.[7] This inward motion of the RV free wall toward the septum is the major contractile movement of the right ventricle.[7,15] Santamore et al.[15] established the importance of the septal-to-free wall shortening and contraction in the transverse direction of the sinus and conus regions. They found that increasing pulmonary arterial pressure in closed-chest, anesthetized, paced dogs with implanted radiopaque markers led to an increase in RV end-diastolic length, an increase in RV pressures, and reductions in cardiac output, percent shortening, and time to maximal velocity of shortening. Although the greatest increases in end-diastolic length occurred in RV free wall-to-septal motion, this increase was not significantly different from that observed in the other dimensions. In addition, although the time to maximal velocity of shortening appeared most markedly prolonged in the septal-to-free wall dimension, this change

was not significant. Other factors that may have contributed to the better correlation between pulmonary arterial systolic pressure compared with regional rather than global RV contraction may be overlap of the right atrium in the region of the conus and passive movement of the pulmonary outflow tract during the cardiac cycle. We also chose to eliminate the portion of the RV apex adjacent to the left ventricle which, although highly contractile, may have included overlap from the left ventricle.

RV systole is characterized by a sequential contraction beginning at the inflow tract and extending into the conal region.[15,22] These 2 embryologically and anatomically different areas can develop markedly different intracavitary pressures during various interventions.[22,23] Whereas a marked intraventricular pressure gradient is measured from sinus to conus, there is a relatively small gradient from conus to pulmonary artery. Thus the infundibular region of the right ventricle may add little to pressure or force generation and may act more as a pressure regulator protecting the pulmonary vasculature.[22] These findings functionally characterize the RV free wall and may partly explain the observed correlation of pulmonary arterial systolic pressure with regional (free wall) but not global RVEF.

RV ejection and systolic pulmonary arterial response: Several studies[24–27] have suggested that RV performance as measured by the RVEF may be closely related to afterload. An important component of RV afterload is pulmonary arterial systolic pressure. Studies[26] have attempted to characterize the relation between global RVEF and pulmonary arterial pressure. Our global as well as total regional RVEF showed some correlation with pulmonary arterial systolic pressure. The best correlation ($r = -0.85$) was found between second-half regional RVEF and pulmonary arterial systolic pressure.

Experimental data support our findings. Simultaneous pressure measurements in the right ventricle and pulmonary artery using high fidelity catheters (Fig. 4) have shown that in early to mid-systole there is a physiologic gradient across the pulmonary valve. This early systolic difference between RV and pulmonary arterial pressure has been termed the *ventricular impulse*.[28] Okino and Spencer[29] reported that in the first 30 to 40% of RV systole, RV pressure exceeds pulmonary arterial pressure and pulmonary arterial flow is accelerated. During the last 60 to 70% of RV systole, RV pressure is less than pulmonary arterial pressure and pulmonary arterial flow decelerates. Dorethy et al.[28] reported the positive RV impulse time in man to be 178 ± 50 ms and the ratio of RV impulse time to right ventricular ejection time to be 0.50 ± 0.13.

It has been shown[30] in isolated canine hearts that the instantaneous relation of RV pressure to volume is as linear as that found in the left ventricle over a wide physiologic range. A striking difference between the ventricles was found in the shape of the pressure-volume loops for ejecting beats. LV pressure-volume loops are nearly rectangular. RV loops are more triangular in shape, with ejection continuing well past peak pressure.[30]

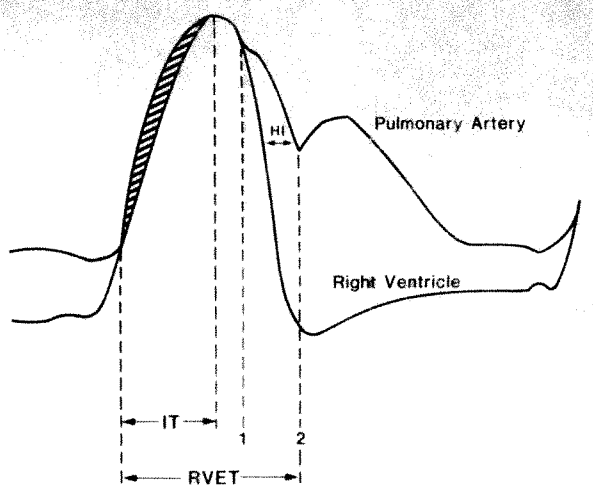

FIGURE 4. Adapted drawing of simultaneous pulmonary artery and RV pressure tracings.[27,29,30,32] The impulse time (IT) is the period of time RV pressure exceeds pulmonary arterial pressure. The **hatched area** represents the positive impulse gradient when acceleration of blood occurs. The hangout interval (HI) is the interval separating the RV pressure curve and the pulmonary incisura.[2] In the later part of systole between point 1 (pressure crossover) and point 2 (pulmonary valve closure), RV pressure is less than pulmonary arterial pressure.

The low resistance and high compliance of the normal pulmonary vasculature are largely responsible for the early peaking of RV pressure and its gradual decline.[30–33] Murgo et al.[32] suggested that inertia is the major component opposing flow or governing the pressure-flow relation across the pulmonary valve in early systole; other factors as resistance and altered compliance become more important later in systole. When pulmonary hypertension results, RV and pulmonary arterial peak pressure occur later in systole with obliteration of the RV pulmonary arterial pressure gradient.[31,32] Patients with pulmonary hypertension also have a marked reduction in the hangout interval,[31,34] the time interval separating the incisura of the pulmonary arterial curve from the RV tracing (Fig. 4). In normal subjects this interval is the last 30 to 90 ms of RV systole.[31]

Clinical utility: A noninvasive predictor of pulmonary arterial hypertension would be helpful in the evaluation and follow-up of acquired as well as congenital heart disease. Measurement of second-half regional RV ejection fraction appears to accurately discriminate normal from elevated pulmonary arterial pressure in the patient group we studied.

We chose not to study patients with atrial fibrillation because of the nonuniformity of their cardiac cycles. Patients with tricuspid regurgitation or RV failure and secondary tricuspid regurgitation were excluded because regurgitation provides a low pressure outlet into the right atrium. Adults with RV outflow obstruction or other right-sided valvular lesions and children were not found in the group available for evaluation. The population studied did include 6 patients with RV volume overload.

Another requirement in this study was that there be an intact RV free wall ejection shell without RV asynergy. This criterion eliminated patients with RV infarction who have had sufficient RV damage to alter contraction and, hence, RVEF. RV asynergy was not commonly seen, even with severe right coronary arterial lesions.[24,35,36] This was evidenced by the inclusion in this study of 4 patients with complete occlusion and 2 patients with 99% stenosis of the right coronary artery.

Implications: A radionuclide technique was used to assess the fractional ejection of blood from the region of the RV free wall during the second half of RV systole. This method detects pulmonary arterial hypertension accurately. However, its application as a quantitative index of pulmonary arterial pressure should be treated more cautiously. Although there is a good correlation between pulmonary arterial pressure and regional RVEF during the second half of systole, small changes in ejection fraction reflect large changes in pressure in the abnormal range. Furthermore, the reproducibility studies suggest that a high degree of technical proficiency is required to apply this method accurately as a quantitative index.

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Effect of Beam Directional Alterations on Left Ventricular Shortening Fraction

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In this study, the dependence on beam direction of the echocardiographically derived fractional shortening of the left ventricular minor axis was evaluated. A directionally oriented, steerable cursor was used to select M-mode lines from a 2-dimensional image at the chordal level. Seven M-mode traces were derived from each image, 1 along the true ventricular meridian and 3 at known deviations on either side of the meridian. M-mode traces, thus derived, all appeared acceptable for measuring wall or cavity dimensions. Results indicate a progressive increase in shortening fraction ($p < 0.05$) for deviations more than 25% of the distance between the meridian and the lateral or medial papillary muscle heads. Decreases in left ventricular dimensions in diastole and systole with progressive deviation from the meridian accounted for the decrease in shortening fraction. Spatial orientation is required for reproducible shortening fraction measurements.

Left ventricular shortening fraction determined with M-mode echocardiography is frequently used as an important indicator of cardiac function.[1-3] Sensitivity and reproducibility of the measurement is generally accepted but not rigorously proved.

Measurements of the left ventricular cavity used to calculate this ratio are usually obtained from M-mode echocardiograms obtained at the chordal level. Proper orientation of the M-mode beam with respect to the long axis of the left ventricle is usually assumed to be standard because chordae tendineae, septum, and the left ventricular posterior wall are imaged simultaneously. This orientation is supposed to provide a minor axis determination.[4] Often, the area providing the best posterior wall recording is considered to be the optimal chord because reflections are thought to return in greatest amplitude from the most perpendicular surface.[5] A minor axis may also be approximated by scanning the left ventricle in a direction perpendicular to the long axis (T scanning)[6] and selecting for measurement the echocardiogram with the largest cavity size. The T-scan, although probably useful, is cumbersome and frequently difficult to accomplish. Furthermore, the largest diameter can not always be assumed to be the meridian if the ventricle is distorted or the plane not truly perpendicular to the long axis.

Limitations of localization exist for an M-mode scan. Transection of a circle (such as the left ventricle) by an M-mode beam produces only 2 points that cannot be

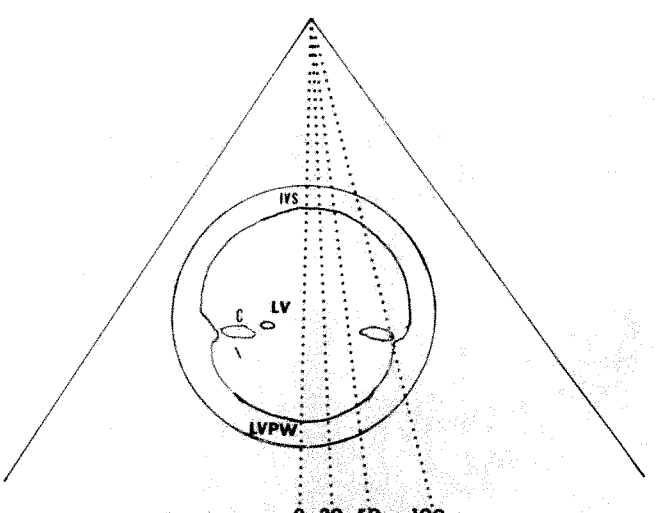

FIGURE 1. Representation of a 2-dimensional short axis image of the left ventricle at chordal level. The **dotted lines** represent the path of the M-mode beam at 0, 20, 50, and 100% deviation from the meridian. C = chordae tendineae; IVS = interventricular septum; LV = left ventricle; LVPW = left ventricular posterior wall.

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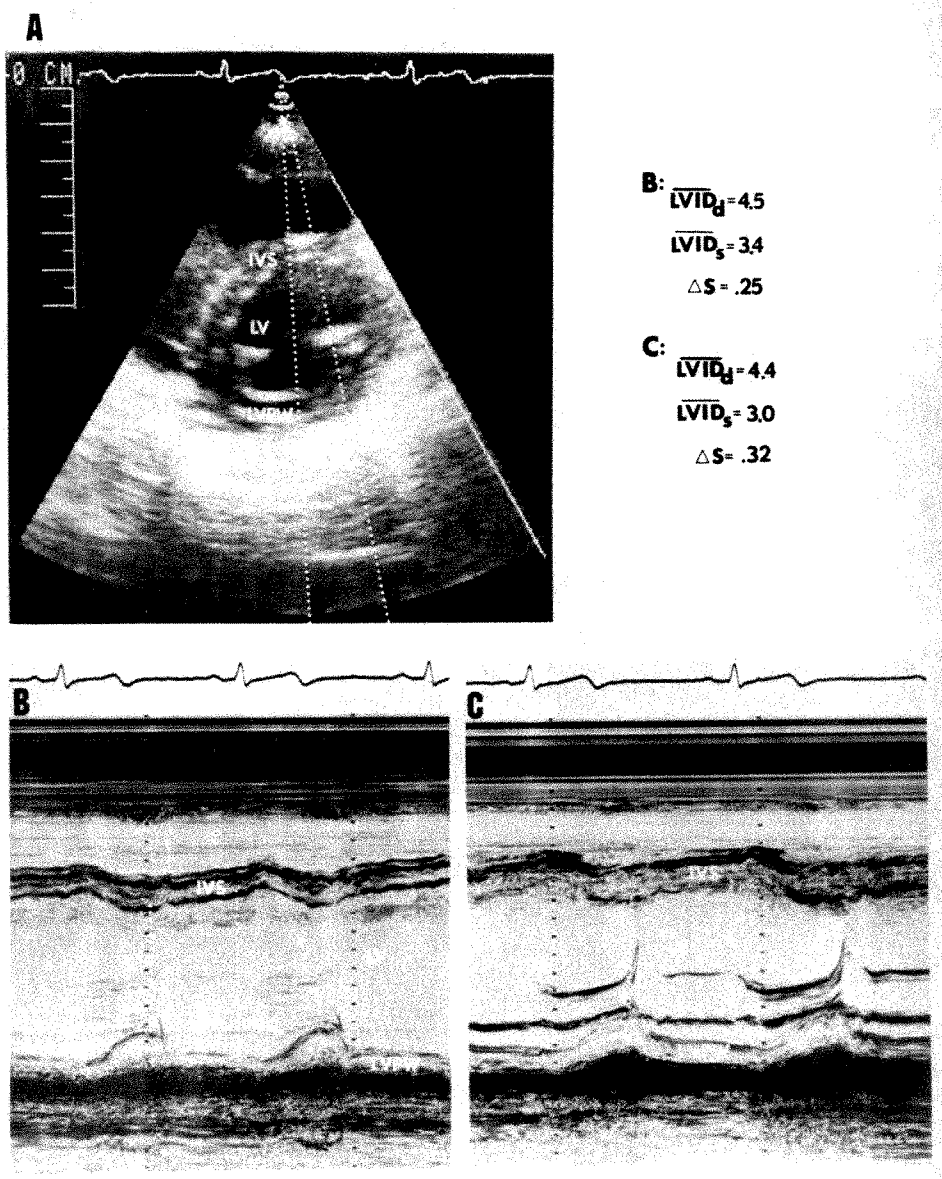

FIGURE 2. Panel A, 2-dimensional short axis image of the left ventricle at the chordal level. The **dotted lines** represent the path of the M-mode beam represented in **panels B and C. Panels B and C** are M-mode tracings recorded from the position of lines B and C in **panel A.** These tracings are acceptable for standard measurements; however, note a slight breakup in the septal endocardium in **panel C.** This may or may not suggest **panel B** is preferable for measurement. Note the change in shortening fraction. The **bottom of the first white dot** is at the leading edge of the septal endocardium. Abbreviation as in Figure 1.

immediately spatially oriented with respect to the true diameter. Also, ultrasonic beams have definite width that causes structural overlap.[7] Clearly, left ventricular cavity dimensions and shortening fraction calculation are dependent on finding the true minor axis diameter.[8] The possibility of recognizing this true minor axis by M-mode echocardiography was the subject of this investigation.

Methods

The patient group consisted of 14 subjects aged 7 to 25 years. Thirteen subjects had normal findings and 1 had rheumatic aortic insufficiency and mitral insufficiency. We used an Electronics for Medicine/Honeywell echocardiograph which allowed nearly instantaneous switching between the mechanical sector 2-dimensional scan and a spatially oriented M-mode from any selected information line. Hard copy records of cross-sectional and M-mode images were made with a Honeywell LS8 recorder. For each subject, a 2-dimensional short-axis image of the left ventricle at the chordal level was obtained. Great care was taken to be certain that this image was 90° to the long axis and that a circular left ventricular image persisted throughout the cardiac cycle. Circularity reasonably assured a plane orthogonal to the long axis. The M-mode cursor was placed at the minor axis meridian (Fig. 1). A freeze frame of the 2-dimensional image was recorded at end-diastole for orientation and documentation, and an M-mode hard copy was recorded of a number of cardiac cycles representative of the cursor location. Hard copies of successive 2-dimensional freeze frames and M-mode samples were taken after deviating the interrogation M-mode line progressively in 4° increments from the meridian, until an acceptable M-mode tracing could not be obtained. Failure occurred when the cursor intercepted either the medial or lateral papillary muscle area in the scan plane just inferior to the chordal level. An acceptable M-mode tracing was defined as successful imaging of chordal structures, both endocardial surfaces of the septum, and endocardial and epicardial surfaces of the left ventricular posterior wall. The appearance of echoes beyond maximal deviation was one of papillary imaging and one of multiple echoes of both septal and posterior endocardial walls

without clear delineation of either structure. Maximal deviation in the right and left direction was defined as full or 100% of the possible geometric deviation. Because angular measurements of the deviation required to lose an acceptable M-mode differed among subjects, the selected M-mode lines from all subjects were normalized with respect to the amount of deviation before imaging papillary muscle landmarks. Lines of interrogation were defined as 0% deviation (meridian), and within the first (20 to 25%), second (26 to 50%), third (51 to 75%), or fourth (76 to 100%) quartile of the available deviation from the meridian. Each quartile represented approximately a 4° successive deviation beginning at the meridian.

Measurements of each M-mode echocardiogram were made according to leading edge methodology, and we also adhered to the other recommendations of the American Society of Echocardiography.[4] Specifically, left ventricular internal dimension in diastole (LVIDd) was measured at the first deflection of the QRS complex. Left ventricular internal dimension in systole (LVIDs) was measured at the point of maximal posterior excursion of the septum. The shortening fraction (ΔS) of each acceptable M-mode echocardiogram was calculated according to the following equation: ΔS = (LVIDd − LVIDs)/LVIDd.[2]

Meridional values of LVIDd, LVIDs, and ΔS were compared by the t test with similarly measured values of chords from the same subject taken from information lines off the meridian.

Results

Eleven of 14 subjects had acceptable images in which septal and left ventricular posterior wall endocardial surfaces could be clearly identified on 2-dimensional and M-mode echocardiographic records. The cursor could be deviated further from the meridian in some subjects than in others and still record an acceptable M-mode echocardiogram. In a few subjects, the left ventricle was imaged more easily on one side of the meridian than on the other.

An acceptable M-mode echocardiographic image could be obtained from information lines that did not pass through the meridian of the ventricle. Figure 2 shows typical M-mode images from locations along and off the meridian. By generally accepted standards,[4] either trace would be suitable for measuring the ventricular cavity at the chordal level.

Figure 3 shows mean results for the 11 subjects with acceptable echocardiograms. A significant decrease in both LVIDd and LVIDs was found when the beam was deviated greater than 50% of the useful perimeter from the meridian. A significant increase in shortening fraction occurred at greater than 31% deviation. At greater than 50% deviation, the shortening fraction increased a mean of 25% above the value at the meridian.

Discussion

The major finding of this study is that the direction of an M-mode beam through the left ventricle cannot be accurately ascertained by qualitative aspects of the M-mode echocardiogram. Images that would be considered acceptable can be recorded off the meridian. A

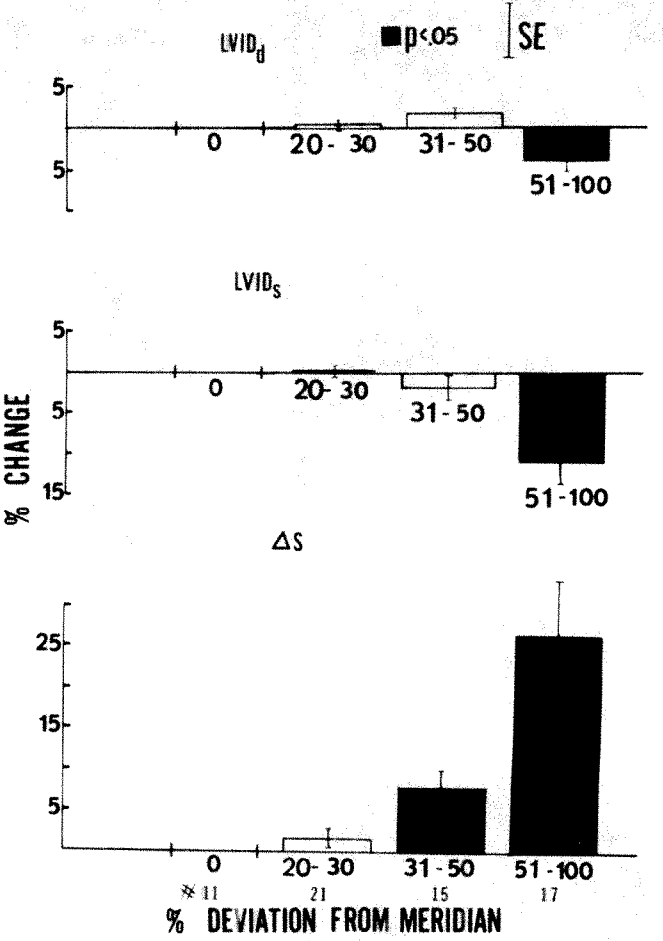

FIGURE 3. Effect on shortening fraction (% change) as the M-mode cursor is deviated from the meridian. The **horizontal axis** shows the percent deviation from the meridian. LVIDd = left ventricular internal dimension in diastole; LVIDs = left ventricular internal dimension in systole; ΔS = shortening fraction; SE = standard error; # = number of measurements.

T scan[6] can be performed to attempt to define the largest dimension in a normally shaped ventricle, but this is time-consuming and difficult in some patients. Further, the assumption that the largest diameter observed on a T scan is the meridian is not necessarily correct, for the transducer may image a plane angled somewhat superiorly or inferiorly from a true short axis. These problems of M-mode echocardiographic orientation can produce significant variation in cavity dimensions and shortening fraction calculations.

The heart as seen on echocardiography with a stationary transducer has cyclic motion in all 3 axes.[9] If the examiner employs extreme care and has awareness of the spatial position shift during the cardiac cycle, it may or may not be possible to track this cardiac motion with 2-dimensional echocardiography so that the same portion of the ventricle is imaged and measured in systole and diastole. Tracking is not possible by M-mode echocardiography alone. M-mode images may detect a

smaller than actual systolic cavity dimension because the ventricle has moved from the diastolic position, even if diastolic size is accurately imaged. The ability to recognize an incorrect image is limited. Although we did not study wall, septal, or right ventricular cavity measurements, our results show a limited ability to be certain that the beam is perpendicular to the structure of interest. Thus, it is possible that these dimensions may also be subject to slant measurement errors.

In summary, this investigation demonstrated that conventional M-mode measurements of left ventricular dimension may be somewhat unreliable because subjectively acceptable, but different, M-mode images may be obtained when the ultrasonic beam is on, or angled off, the true ventricular meridian. Measurements of the left ventricular internal dimension will vary depending on the angle. Accordingly, a derivative of cavity measurements such as shortening fraction or ejection fraction can change as a function of the angle. Also, the dimensional change may be due to the additional problem of locating the same portion of the cavity for measurement in systole and diastole. These problems reduce the usefulness of M-mode measurements, especially those which depend on subtracting systolic dimension from diastolic dimension. This investigation suggests that M-mode records derived from 2-dimensional images or measurements on the 2-dimensional image provide more assurance that a measured dimension represents the actual value.

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Low Energy Countershock Using an Intravascular Catheter In an Acute Cardiac Care Setting

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We examined the feasibility, effectiveness, and safety of using an intravascular catheter positioned in the right ventricular apex for countershock in a coronary care unit setting in 8 patients who had recurrent ventricular tachyarrhythmia. Countershock using 2.5 to 40 J stored energy (damped sinusoidal wave form) was attempted 115 times to terminate 100 episodes of ventricular tachyarrhythmia (ventricular tachycardia, 91; ventricular flutter, 3; ventricular fibrillation, 6). Eighty-six (87%) of 99 countershock attempts for ventricular tachycardia, 3 (60%) of 5 for ventricular flutter, and 4 (36%) of 11 for ventricular fibrillation were successful using this technique. The catheters remained in stable position for 1 to 16 days without dislodgment. A majority of the countershocks were delivered by the regular nursing staff in the coronary unit.

We conclude that low energy countershock through an intravascular catheter system is feasible, safe, and effective in a coronary care unit setting. Such a system should be beneficial in the acute management of patients who have recurrent ventricular tachycardia or fibrillation. The catheter lead may also prove useful in managing ventricular tachyarrhythmias that occur during electrophysiologic studies.

Patients with unstable cardiac disease may experience frequently recurring ventricular arrhythmias requiring repeated external countershock while appropriate medical management is being instituted. Repetitive countershocks can be psychologically and physically traumatic for these patients and may be associated with a risk of further myocardial necrosis.[1] The pressure on the medical staff to control arrhythmias quickly under these circumstances may result in the overzealous use of antiarrhythmic agents with increased risk of drug toxicity.

We studied the feasibility, effectiveness, and safety of using an intravascular catheter lead system to help control arrhythmias in 8 patients referred for management of frequently recurring, sustained ventricular tachyarrhythmia. In particular, we assessed the usefulness of this catheter system for overdrive termination of ventricular tachycardia, low energy cardioversion, and defibrillation and temporary pacing in the event of bradycardia.

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Methods

Patients: All patients were referred to the Coronary Care Unit at University Hospital for the management of recurrent ventricular tachycardia or fibrillation requiring 1 to 20 external countershocks before transfer (Table I). Prior approval for the use of the countershock catheter in such patients was obtained from the Ethics Committee at The University of Western Ontario. Written, informed consent was obtained from each patient. All 8 patients were men, aged 35 to 63 years. Six patients had coronary heart disease (2 with acute myocardial infarction) and 2 patients had cardiomyopathy. Six of these 8 patients developed ventricular arrhythmia requiring countershock.

Description of the catheter system: The countershock lead (Medtronic, DFX-2) is a tripolar 9.5Fr, 100 cm polyether urethane catheter (Fig. 1) with a central lumen for guide wire manipulation. The catheter has 4 stainless steel electrode sleeves, each with a surface area of 125 mm^2. The most distal electrode sleeve (A) is located at the catheter tip, and a second

TABLE I Patient Population Data

Case	Age (yr) & Sex	Weight (kg)	Diagnosis	External CS Attempts	CTR	Lead Duration (Days)	R Wave (mV)	VTA Episodes Requiring Catheter Lead CS			
								VT	VFL	VF	Total
1	58M	75	CAD, LV aneurysm	4	0.46	5	5	2	1	...	3
2	57M	63	AMI, LV aneurysm	9	0.52	16	20	78	...	4	82
3	56M	82	AMI	20	0.57*	1	5.3	1	2	2	5
4	40M	61	Cardiomyopathy	3	0.51*	9	2	1	...	...	1
5	63M	70	CAD, LV aneurysm	6	0.60	11	15	7	...	...	7
6	55M	79	CAD	1	0.51*	1	5	...	...	...	0
7	35M	57	Cardiomyopathy	2	0.54	1	1.7	...	...	...	0
8	63M	73	CAD, LV aneurysm	1	0.48	1	3.6	2	...	...	2
Total	...	...	...	...	...	...	...	91	3	6	100

* Portable chest roentgenogram.

AMI = acute myocardial infarction; CAD = coronary artery disease; CTR = cardiothoracic ratio; External CS = number of transthoracic countershock attempts before insertion of lead; R wave = R-wave amplitude measured from catheter distal electrode; VF = ventricular fibrillation; VFL = ventricular flutter; VT = ventricular tachycardia; VTA = ventricular tachyarrhythmia.

electrode sleeve (B) is located 5 mm proximally. The other 2 sleeves, separated by a distance of 5 mm (C and D), are located 100 mm from sleeve B and constitute a single electrode. Each electrode is connected by a separate conductor coil wire to 1 of 3 connector pins at the proximal end of the catheter. In situ, the distal electrodes (A and B) are positioned in the right ventricular apex and the proximal electrode sleeves (C and D) are located approximately at the junction of the superior vena cava and the right atrium (Fig. 2). The distal poles A and B can be used as a bipolar pacing pair. For defibrillation and cardioversion, electrodes A and B become common (the cathode) and the proximal electrodes (C and D) become the anode.

The catheter was inserted employing a standard percutaneous introducer into the left subclavian vein and advanced using fluoroscopy to the right ventricular apex. After insertion, the amplitude of the R wave recorded from the distal electrodes (A and B) was measured daily as one index of lead dislodgment, using a Medtronic 5300 pacing system analyzer. Lead position was verified every 12 to 24 hours by a chest radiograph (Fig. 2).

The lead was then interfaced to a commercially available Hewlett-Packard 78619A defibrillation unit, which produces a damped sinusoidal discharge wave form, through a switch box and current attenuator constructed in the University Hospital Biomedical Engineering Department. A programmable stimulating device or temporary pacemaker was connected to the distal electrode pair by the switching box.

Protocol: Coronary care unit nurses and house-staff were instructed in the proper operation of the unit before each change of shift. Upon recognition of sustained ventricular tachyarrhythmia, the staff was instructed to deliver shocks in incremental doses until successful reversion to sinus rhythm occurred. Energy levels 2.5, 5.0, 7.5, 10, 15, 20, 30, and 40 J were

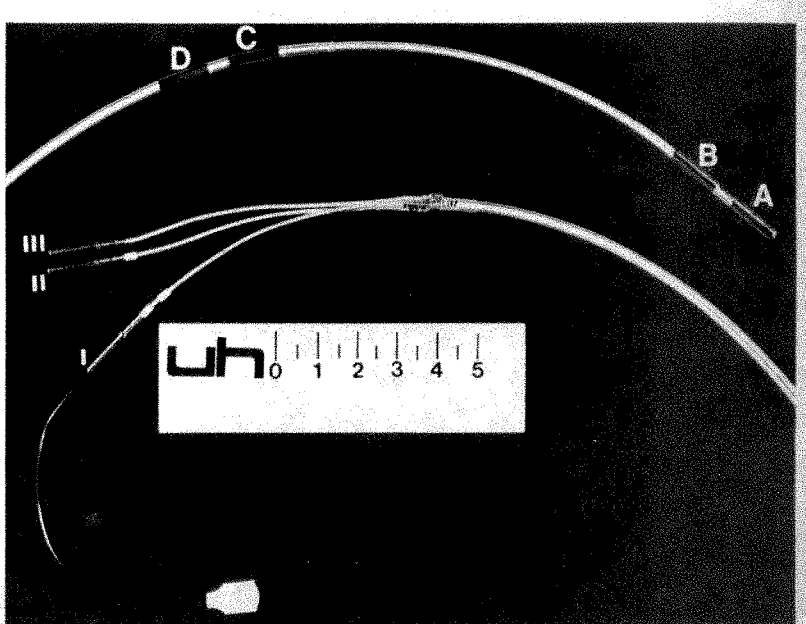

FIGURE 1. Tripolar countershock catheter. A = distal right ventricular electrode sleeve; B = proximal right ventricular electrode sleeve; C and D = proximal superior vena cava/right atrial electrode sleeves; I = distal right ventricular electrode connector pin; II = proximal right ventricular connector pin; III = superior vena cava/right atrial electrode connector pin (see text).

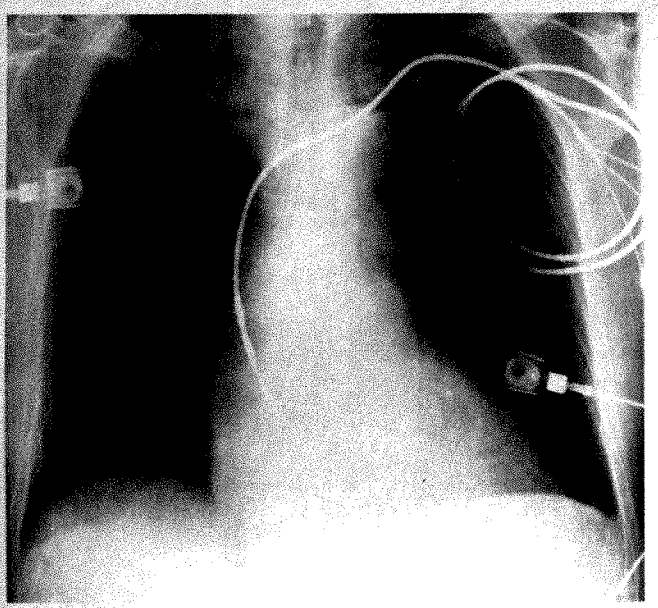

FIGURE 2. Chest roentgenogram illustrating proper placement of tripolar lead with the catheter tip in the right ventricular apex and proximal electrode at the junction of the right atrium and superior vena cava.

TABLE II Analysis of Countershock Attempts With Intravascular Lead*

Case	Total Attempts		Energy Dose (J) 2.5–5.0	7.5–10	15–40
1	VT	2	2/2	...	...
	VFL	3	0/2	1/1	...
2	VT	84	1/2	73/80	0/2
	VF	5	1/1	0/1	2/3
3	VT	1	0/1	...	...
	VFL	2	...	...	2/2
	VF	6	0/1	...	1/5
4	VT	1	1/1	...	...
5	VT	8	7/8	...	...
6	...		...	...	...
7	...		...	...	...
8	VT	3	1/2	...	1/1
Totals	VT	99	12/16	73/80	1/3 = 86/99 (87%)
	VFL	5	0/2	1/1	2/2 = 3/5 (60%)
	VF	11	1/2	0/1	3/8 = 4/11 (36%)
		115	13/20 (65%)	74/82 (90%)	6/13 (46%)

* Numerators = number of successful countershock attempts at specified energy dose; denominators = total number of countershock attempts delivered; VF = ventricular fibrillation; VFL = ventricular flutter; VT = ventricular tachycardia.

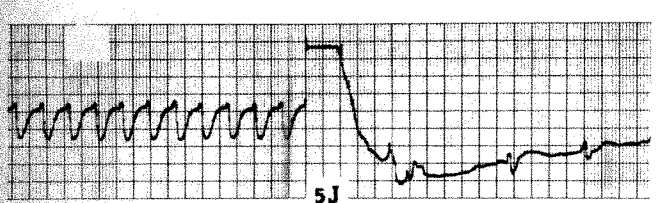

FIGURE 3. Patient 2. Cardioversion using intravascular catheter countershock at 5 J. A lead II monitor strip shows 11 beats of ventricular tachycardia. A synchronized 5 J discharge is delivered, restoring sinus rhythm.

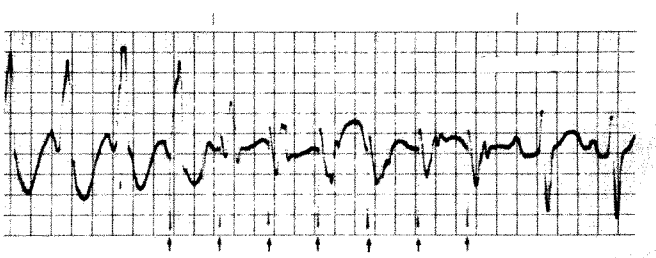

FIGURE 4. Patient 5. Burst ventricular pacing using countershock catheter. Ventricular tachycardia at cycle length 520 ms is entrained by pacing stimuli (**arrows**) at a cycle length of 500 ms. Abrupt termination of pacing results in restoration of sinus rhythm.

chosen and delivered in the synchronized (for ventricular tachycardia and flutter) or nonsynchronized mode (ventricular fibrillation). A second conventional Hewlett-Packard 78619A defibrillator was available for back-up transthoracic shocks.

The initial energy dose selected was 5 J for ventricular tachycardia and flutter, while defibrillation attempts for ventricular fibrillation started at 10 J. After 5 consecutive successful attempts, the coronary care unit staff was instructed to reduce the energy used to the next lower level. However, if any failures occurred, the dose was doubled and not reduced until 5 consecutive successful attempts were attained. While every attempt was made to adhere to this protocol, use of transthoracic countershock at any earlier time was left to the discretion of the staff at the bedside based upon the clinical status and hemodynamic stability of the patient during tachycardia.

"Burst" pacing through the catheter was attempted in 1 patient (Patient 5) with recurring episodes of ventricular tachycardia using a stimulus cycle length of 500 ms and current output of 15 mA.

Serial measurement of serum creatine kinase, lactic dehydrogenase, or glutamic oxaloacetic transaminase as an index of possible myocardial injury secondary to catheter countershock was not conducted. We could not reliably attribute elevations in enzyme levels to this technique since patients had received transthoracic countershock before insertion of the catheter and some had had an acute myocardial infarction.

Results

The catheter was inserted in 8 patients (Table I). Lead insertion was carried out uneventfully in the coronary care unit (5 patients) or in the electrophysiology laboratory (3 patients). Leads remained in position 1 to 16 days without a single lead displacement. Six of the 8 patients developed ventricular tachyarrhythmia requiring use of the countershock catheter.

Ventricular tachycardia: Synchronized cardioversion was attempted 99 times for 91 episodes of ventricular tachycardia (Fig. 3, Table II). Eighty-six (87%) of these attempts successfully terminated tachycardia using energy levels of 10 J or less. In 1 patient burst ventricular pacing was utilized to terminate ventricular tachycardia and was successful in 10 of 14 attempts (Fig.

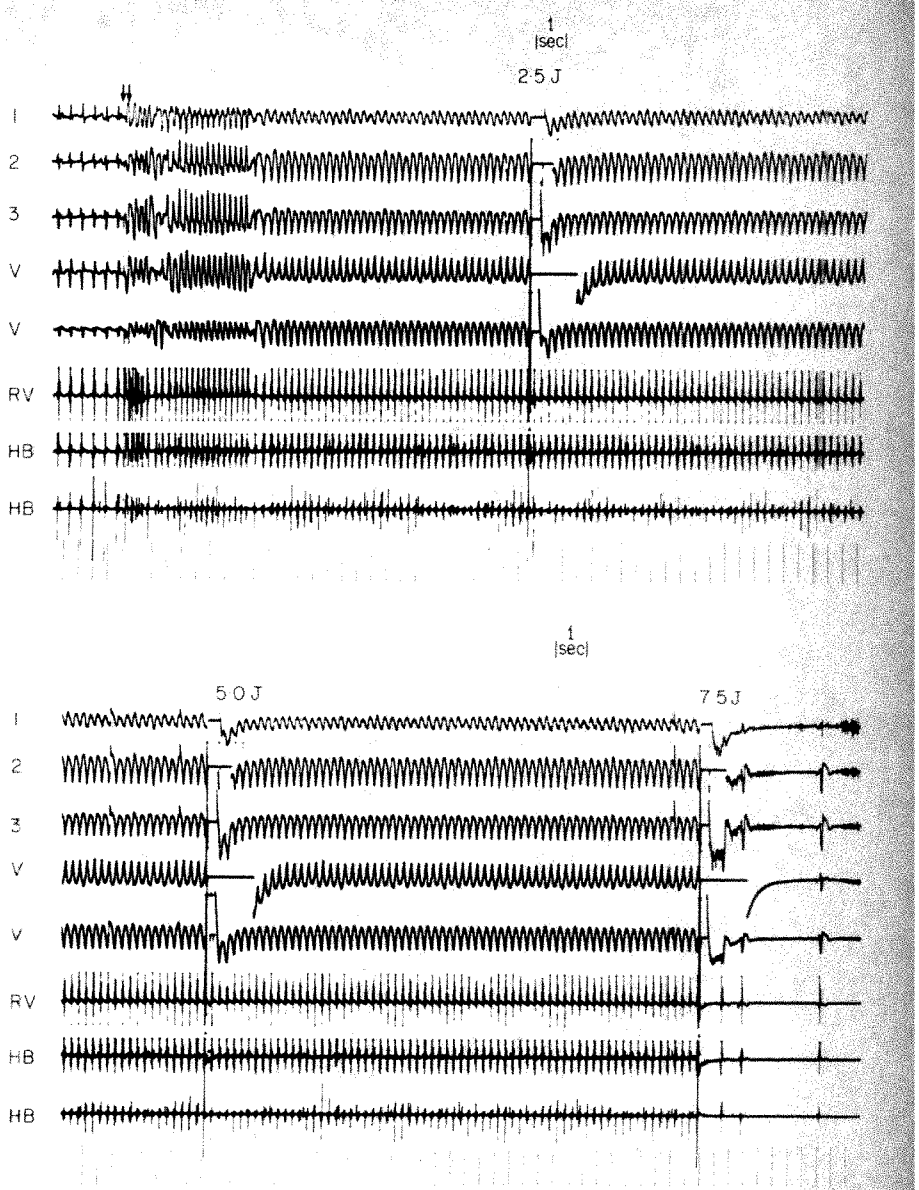

FIGURE 5. Continuous intracardiac recordings of ventricular tachycardia at electrophysiologic study. **Top,** the recording begins with ventricular tachycardia. The introduction of 2 premature ventricular stimuli (**arrows**) to terminate the tachyarrhythmia results in acceleration followed by a change in morphology of the tachycardia and hemodynamic deterioration. Catheter countershock attempt using 2.5 J fails to terminate ventricular tachycardia. **Bottom,** a second attempt using 5.0 J delivered through catheter lead also fails, but 7.5 J energy dose terminates ventricular tachycardia and restores sinus rhythm.

4). However, the use of programmed ventricular extrastimuli to terminate stable ventricular tachycardia in another patient led to acceleration of tachycardia with hemodynamic collapse (Fig. 5, top), necessitating the use of cardioversion by means of the catheter (Fig. 5, bottom).

Energy doses of 10 J or less failed to terminate 3 episodes of ventricular tachycardia (Patients 2, 3, and 5) and 2 other episodes did not terminate after 20 J (Patient 2). Transthoracic cardioversion using 200 J converted all 5 episodes.

Ventricular flutter and fibrillation: All 3 episodes of ventricular flutter occurring in 2 patients were converted with synchronized shocks of 7.5 J in 1 and 15 J in the other after a total of 5 attempts (Table II). There were 6 episodes of ventricular fibrillation requiring 11 attempts at catheter countershock. Four episodes were successfully terminated (Fig. 6), 1 at 5 J and 3 at 40 J. In 1 of the 2 failures (Patient 2), conventional defibrillation at 400 J successfully restored sinus rhythm. The second failure involving Patient 3 occurred as a preterminal event. Several attempts at conventional countershock in this patient resulted in asystole. In spite of successful pacing using an indwelling catheter, no cardiac output could be obtained.

Discomfort associated with catheter defibrillation: Discomfort was difficult to assess because most patients had a diminished level of consciousness at the time of countershock. However, shocks of 2.5 J were associated with a visible chest thrusting. One patient described a 2.5 J countershock as a "kick in the chest."

Clinical outcome: Satisfactory arrhythmia control was ultimately obtained in all 6 surviving patients. Two patients died in hospital with the catheter lead in situ. At the time of death, the lead was in satisfactory posi-

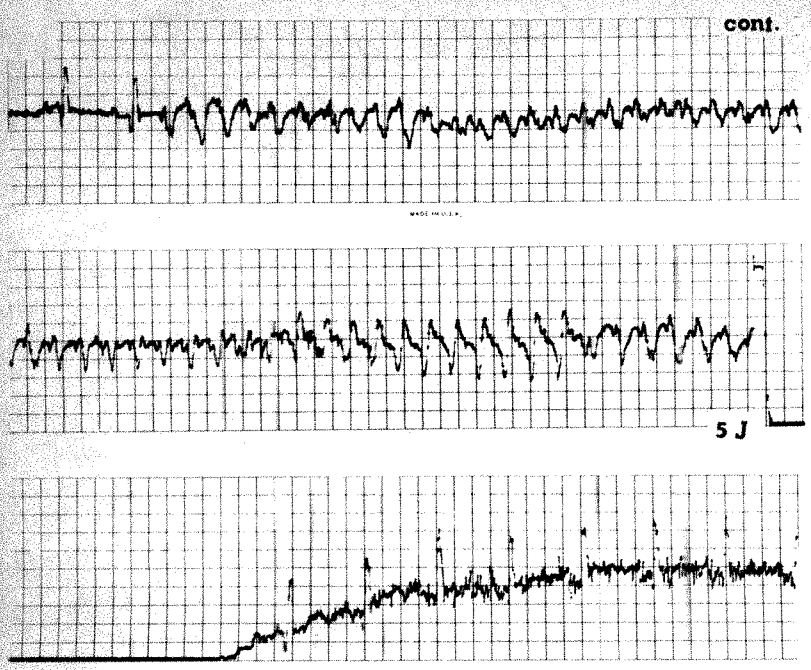

FIGURE 6. Patient 2. A continuous rhythm (lead II) strip shows sinus rhythm initially, with spontaneous development of ventricular fibrillation. Delivery of 5 J nonsynchronized shock using the catheter lead restores sinus rhythm.

tion in the right ventricular apex in both patients despite prolonged attempts at cardiopulmonary resuscitation. In 1 patient (Patient 3), a focal area of endocardial hemorrhage measuring less than 2 mm^2 was visible at the site of the proximal electrode (C and D). No gross or microscopic injury could be identified at the right ventricular apex. This patient had received 9 countershocks (25 to 40 J). The second patient had no identifiable injury as a result of 8 countershocks (2.5 to 5.0 J).

Discussion

Advantages of method: Patients with frequently recurring sustained ventricular tachyarrhythmia may require repeated cardioversion or defibrillation while effective antiarrhythmic management is being instituted. We have shown that the use of low energy countershock delivered through an intravascular catheter lead is feasible, effective, and safe in this setting. The countershock lead can be inserted with the relative ease of a temporary pacing lead and remains stable after initial placement. The system described offers several advantages over the conventional method of countershock. First, relatively low energy levels can be used with a potential for less myocardial necrosis after repeated countershocks.[1] Second, the catheter can be connected to a programmable stimulator for conversion of ventricular tachycardia by burst pacing or ventricular extrastimuli. Defibrillation can be carried out through the catheter in the event of acceleration of tachycardia. Third, the catheter can be used for pacing in the event of bradycardia or asystole. Finally, defibrillation can be carried out expediently with the patient in any position without the delay of placing paddles. Finally, low energy countershock is probably less traumatic to the still-conscious patient with deteriorating cardiac output than conventional countershock.

It is certain that the energies used for countershock in this study were greater than the minimal required energies using the catheter system.[2,3] Using our countershock system, we could not be certain of accuracy using stored energy less than 2.5 J. Furthermore, most countershocks were delivered by intensive care nursing personnel who could not be asked to titrate the minimal energy in patients with hemodynamic deterioration.

Comparison with previous lead systems: In 1970, Mirowski et al.[4] introduced the concept of an automatic internal defibrillator and conceived a lead system wherein a catheter placed at the right ventricular apex had 1 electrode in the right ventricle and a second separate electrode consisting of an apical subcutaneous plate. Subsequent designs incorporated both electrodes onto a single catheter,[5,6] and studies with various electrode positions demonstrated that the greatest efficacy of defibrillation was obtained when the distal electrode was placed in the right ventricular apex.[7] The optimal position of the proximal electrode (whether in the high right atrium or superior vena cava) was less critical so long as sufficient electrode surface area was present. However, in a review of their experience with the catheter mounted bielectrode lead, Mirowski et al.[8] noted that lead dislodgment was a significant problem leading to failure to defibrillate. We did not encounter lead displacement with the catheter (Medtronic DFX-2) used in this study. Newer prototypes of this catheter using fixation systems should minimize the problem of dislodgment.

Implications: Low energy countershock using an intravascular catheter is feasible in a clinical setting. Pacing, programmed stimulation, cardioversion, and

defibrillation can be performed with the catheter, resulting in more expedient arrhythmia management. In addition to its usefulness in the acute care setting, this technique could be adapted for use during electrophysiologic studies where ventricular tachyarrhythmia is anticipated. Finally, the potential exists for a completely "automated" bedside unit connected to the defibrillating catheter capable of detecting and treating both bradyarrhythmia and ventricular tachyarrhythmia.

Acknowledgment

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Intraoperative 2-Dimensional Echocardiography: Ejection of Microbubbles From the Left Ventricle After Cardiac Surgery

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Although the presence of entrapped air in the left ventricle at surgery has long been a concern, its prevalence and clinical significance are unknown. Two-dimensional echocardiography provides a unique means for observing intracardiac microbubbles intraoperatively. Accordingly, intraoperative 2-dimensional echocardiograms obtained in 79 patients immediately after cardiopulmonary bypass were examined for the presence of microbubbles. Left ventricular microbubbles were detected in 14% of coronary artery bypass operations (n = 22), 50% of multiple valve replacements (n = 8), 67% of single valve replacements (n = 58), and 100% of atrial septal defect closures (n = 4), left atrial myxoma resections (n = 2), and mitral commissurotomies (n = 2). Microbubbles were not observed in patients undergoing coronary artery bypass with valve replacement (n = 4) or with removal of left ventricular aneurysm (n = 1). Continuous ejection of microbubbles from the left ventricle was frequently noted for extended periods of time and, although no patient in this study showed evidence of gross neurologic dysfunction, the possibility of subclinical organ damage exists. We conclude that 2-dimensional echocardiography is useful for detection of intracardiac microbubbles and therefore may be instrumental in their elimination.

Air embolism is a dreaded complication of cardiac surgery.[1] The potential for embolism from both the cardiopulmonary bypass circuit and residual air in the left side of the heart appears to have been reduced by improved equipment and surgical techniques.[1] Nevertheless, the incidence of this problem might be further reduced by improved methods for detection of residual air in the left heart. The frequency and effects of air emboli have been studied in both clinical[2–4] and experimental[5–8] settings. Methods have included reflected[5] and Doppler ultrasound,[3] and direct visualization of the interior of the beating heart.[5] Unfortunately, many of these techniques necessitate apparatus too complex or invasive for routine intraoperative use. With others, sensors in the peripheral circulation may give inaccurate measurements due to streaming or dilution. Air is a high contrast medium in echocardiograms because of the difference in acoustic properties between air and blood.[9] Consequently, pulsed echocardiographic and A-mode and M-mode recordings have all been shown to be sensitive in detecting air microemboli, and intraoperative M-mode echocardiography has shown promise for detecting residual intracardiac air.[10] Two-dimensional echocardiography, however, allows visualization of the entire cross-section of the left ventricle in a single image, and image clarity is sufficient for detection of intracardiac air and microbubbles without specialized training.[11] Accordingly, in the present study, intraoperative 2-dimensional echocardiography was employed in 79 patients to determine the prevalence and clinical effects of residual air in the left ventricle at the conclusion of cardiac surgery.

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Methods

Echocardiography during surgery: Informed consent for intraoperative echocardiography was obtained in 79 patients before cardiac surgery. Two-dimensional echocardiograms were recorded immediately before and after cardiopulmonary bypass with the patient cannulated as a precaution against arrhythmia. However, no intraoperative arrhythmias or other complications resulted. Images were obtained with a gas-sterilized hand-held 3.5 MHz phased-array ultrasound transducer and a V-3000 or V-3400 Ultrasonograph (Diasonics, Sunnyvale, California). Both short- and long-axis views of the left ventricle were recorded on videotape and examined later for the quantities of microbubbles. The transducer was gently applied to the anterior wall of the right ventricle, without a water path or deliberate introduction of fluid into the pericardium.[11] With experience, image recording could routinely be completed in less than 2 minutes. Myocardial preservation during surgery was provided by cold potassium cardioplegia.[12] Techniques for evacuation of air from the left side of the heart included decompression of the mitral valve, venting through the right superior pulmonary

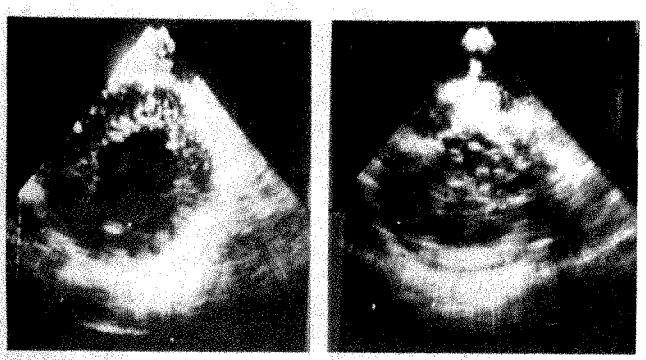

FIGURE 1. Microbubbles are illustrated in the left ventricle in 2-dimensional short-axis echocardiogram obtained at the conclusion of cardiopulmonary bypass after mitral and aortic valve replacement (**right panel**). Short-axis echocardiogram before surgery does not demonstrate this phenomenon (**left panel**).

vein, and final closure of atriotomies beneath a fluid level.[1] A small needle was placed in the ascending aorta and allowed to drain freely as left-sided cardiac output resumed at the conclusion of surgery to provide protection against possible air embolism.[1]

Echocardiographic interpretations: Microbubbles were apparent on intraoperative echocardiograms as bright reflections swirling within the lumen of the left atrium and left ventricle on short-axis sections and passing progressively from the left atrium to the left ventricle to the aorta on long-axis sections. The prevalence of air in the left heart was graded 0 to 3+ (0 = no air; 1+ = less than 5 microbubbles per frame; 2+ = moderate quantities of microbubbles, 10 to 25 per frame; 3+ = severe quantities of microbubbles, usually too many to count). The minimum number of bubbles detected in any study receiving a positive designation was 5. Echocardiograms before bypass were compared with those after bypass to facilitate accurate differentiation of air bubbles from artifacts.

Differences in surgical technique which might affect the prevalence of microbubbles were noted, and charts were reviewed for evidence of postoperative neurologic difficulty. The latter data were obtained retrospectively, and detailed neurologic examinations were not performed.

Results

Prevalence and severity of intraoperative microbubbles (Table I, Fig. 1): Overall, residual microbubbles were detected at the conclusion of cardiac surgery in 39 of the 79 patients (49%), and the prevalence of microbubbles was judged moderate or severe in 20 (25%). Microbubbles were detected in 14% of coronary artery bypass cases (n = 22), 67% of single valve replacements (n = 36), 50% of multiple valve replacements (n = 8), and 100% of atrial septal defect closures (n = 4), mitral commissurotomies (n = 2), and resections of left atrial myxoma (n = 2). Microbubbles were not observed in any patient undergoing combined procedures (coronary bypass plus valve replacement [n = 4] or plus left ventricular aneurysm resection [n = 1]). In some cases, microbubbles were detected being continuously ejected from the left ventricle for 5 minutes or longer after cardiopulmonary bypass, but the time course of microbubble concentration was not systematically studied.

TABLE I Prevalence of Microbubbles After Cardiac Operations

	Grading of Microbubbles				Patients	
Operation	0	1+	2+	3+	n	%
CABG	19	3	0	0	22	14
AVR	9	7	9	1	26	65
MVR	3	3	3	1	10	70
MC	0	0	1	1	2	100
XVR	4	2	0	2	8	50
ASD	0	3	1	0	4	100
LA myxoma	0	1	1	0	2	100
CABG + valve replacement	4	0	0	0	4	0
CABG + aneurysm	1	0	0	0	1	0
Total	40	19	15	5	79	49

Aneurysm = left ventricular aneurysm resection; ASD = atrial septal defect; AVR = aortic valve replacement; CABG = coronary bypass; LA = left atrial; MC = mitra commissurotomy; MVR = mitral valve replacement; XVR = multiple valve replacement.

Procedures requiring direct opening of the left atrium or left ventricle displayed the preponderance of intraoperative microbubbles. All patients receiving a 3+ designation underwent either aortic valve replacement, mitral valve replacement, double valve replacement involving at least 1 of these 2 valves, or mitral commissurotomy. All of the valve operations in which microbubbles were detected were left-sided procedures; no microbubbles were found in the 1 case of simple tricuspid valve replacement. No microbubbles were visualized in the left atrium or left ventricle before cardiopulmonary bypass, even with simultaneous cardiac output determinations producing clouds of microbubbles in the pulmonary artery. No large collection of residual air as a single bubble of substantial size was observed.

Correlation with surgical technique and methods of decompressing the heart: In general, surgical techniques were similar during valve replacements and differences could not be correlated with the degree of microbubbles present. Procedures utilized to decompress the left heart during coronary bypass were related to postoperative microbubbles as follows: 2 coronary bypass patients were vented with a catheter in the right superior pulmonary vein. Of these 2, rare microbubbles were subsequently detected in 1. A small number of microbubbles was also detected in 2 of 17 patients in whom decompression for coronary bypass was provided by suction on a cardioplegia needle in the ascending aorta.

Retrospective chart review demonstrated that during the period of this study no patient had neurologic impairment significant enough to be detected on routine physical examination, subjectively by the patient, or by the patient's family.

Discussion

Safety and sensitivity of technique: The present results demonstrate that intraoperative 2-dimensional echocardiography is a safe, convenient, and highly sensitive technique for detection of microbubbles in the

left ventricle at the conclusion of cardiac operations. This observation confirms previous conjecture based on M-mode echocardiography[10] and is consistent with previous clinical observations.[2–4] Indeed, it appears that the sensitivity of echocardiography in this regard is excessive, since no patient studied developed gross neurologic changes, even among those with continuous clouds of microbubbles ejected into the aorta (Table I). However, it has long been recognized that neurologic changes resulting from cardiac surgery may not be detected unless specific objective testing is employed.[13,14] Thus, at present it is not known whether the observation of clouds of microbubbles in the left ventricle is of clinical significance, although contrary observations have been reported.[3] Indeed, deliberate injection of microbubbles is the source of the "echocardiographic contrast effect" used to detect intracardiac shunts in neonates.[9,15] The quantity of microbubbles employed for clinical studies, however, appears small in comparison with the prolonged ejection of echo clouds in some of our patients. Moreover, since these microbubbles are too large to traverse normal capillary beds, they may produce some deficits, and it would be clearly desirable to strive to eliminate them. The lower limit of bubble size visible to ultrasound has been estimated to be 2 to 125 μm.[3,8,9,16]

Cause of microbubbles: Since intraoperative microbubbles are most prevalent when air must be admitted to the left atrium or left ventricle (for mitral or aortic valve replacement) and of low prevalence and in small amounts after coronary bypass, it is most probable that the bubbles represent foam which accumulates on the walls of the left ventricle, left atrium, and pulmonary veins[17] when they are refilled with blood. Consistent with this view, prior experimental studies have visualized small residual collections of air in the left ventricle of dogs during cardiac surgery.[5] A variety of possible wetting agents have been tested to reduce the prevalence of this problem, with paraldehyde the most effective of those applicable clinically.[5] Previous observations of intracavitary echoes early after mitral valve replacement may also represent microbubbles[18]; however, the effect we have observed usually disappears within 60 minutes after the conclusion of cardiopulmonary bypass.

Inconsistent with this view of the cause of microbubbles is our low observed incidence of the problem after operations combining coronary bypass with valve replacement or aneurysm resection. Since these procedures require increased duration of bypass between the time the heart is closed and all coronary anastomoses are completed, we speculate that all of the microbubbles present had been ejected from the heart before our echocardiographic studies. Since the number of patients in this group is small, the observations may not be representative.

Possible limitations of technique: The present results also suggest that intraoperative echographic studies might detect large bubbles of air in the left heart which could be aspirated or vented before left ventricular output is allowed to resume. We have not documented such a situation clinically, however. Finally, intraoperative 2-dimensional echocardiography is constrained by certain limitations for this purpose. Specifically, adequate images of the left heart require the presence of blood in the right ventricle, which serves the purpose of a stand-off and water path. For centers employing a double-cannulation technique, as we do, the presence of air in the right ventricle or a collapsed right ventricle, or both, will interfere with satisfactory imaging unless total bypass is converted to partial bypass or air is evacuated from the right ventricle by other measures.

Implications: Intraoperative 2-dimensional echocardiography is a sensitive method for detection of microbubbles ejected from the left ventricle at the conclusion of cardiac surgery, and appears promising for detection of larger amounts of air with lethal potential. The presence of microbubbles is most closely related to valve surgery requiring entry of air into the left ventricle. Although no clinical evidence of neurologic deficit was apparent in patients in this study, it would seem desirable to devise measures to limit the presence of postoperative microbubbles.

Acknowledgment

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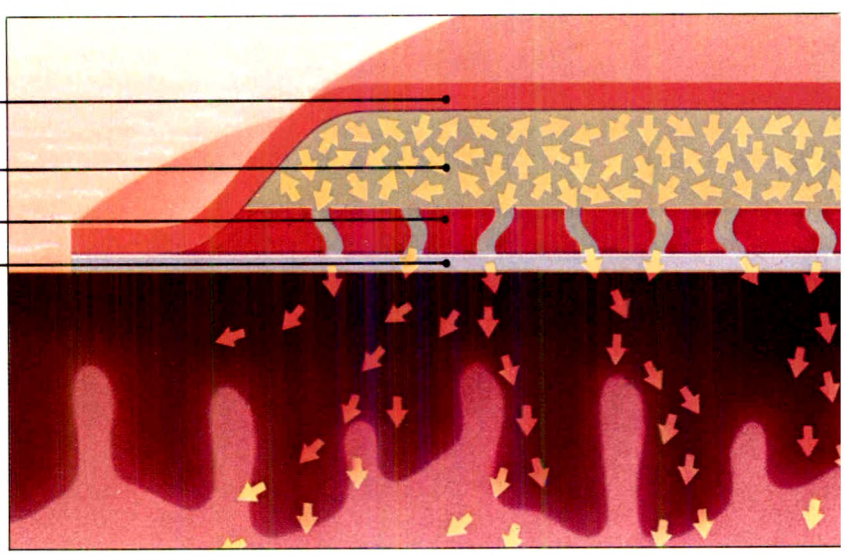

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Constant protection against angina attacks assured by uninterrupted plasma concentrations of nitroglycerin: Transderm-Nitro 5 rated to release 5 mg/24 hours; Transderm-Nitro 10 rated to release 10 mg/24 hours.

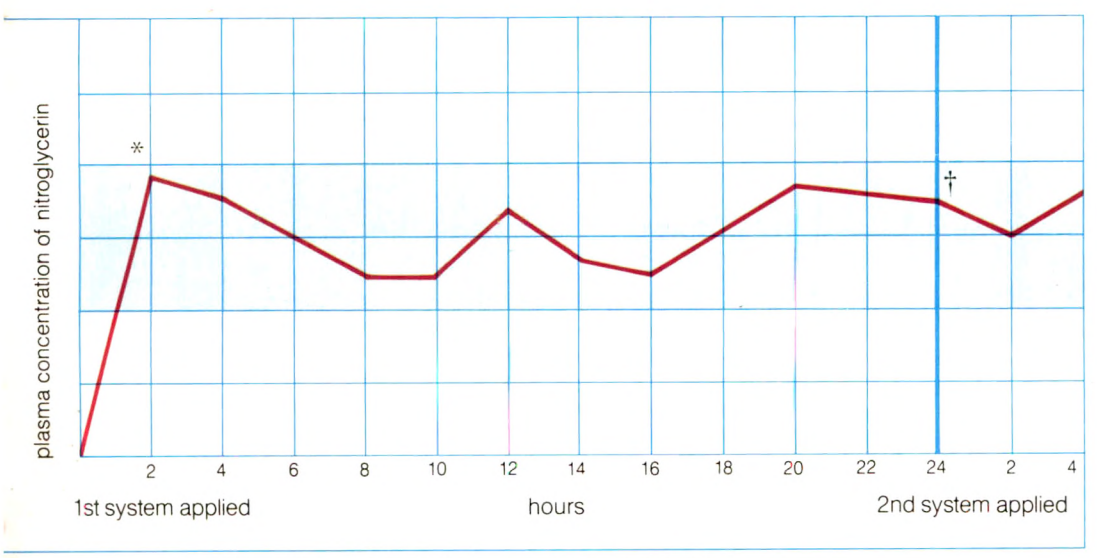
Orthostatic hypotension may indicate nitroglycerin overdosage; reduce dosage if symptoms occur. Nitrates are contraindicated in patients with increased intraocular pressure. Withdrawal should be gradual if treatment is terminated. Do not apply to distal parts of the arms and legs.

System is simple and easy to use

- Every 24 hours the old system is removed and the new one applied.
- Therapeutic effect can be anticipated 30 minutes after application and maintained for 30 minutes following removal.
- Can be applied anywhere on the body except the distal extremities.

An advance beyond tablets and ointments

- 24-hour sustained therapeutic blood levels of nitroglycerin
- Precise dosage control
- Ease of administration...avoids mess and inconvenience of ointments
- Once-a-day dosage to enhance compliance
- May be worn while swimming, bathing and showering



*1st measurement in this study was taken 2 hours. However, a therapeutic effect can be anticipated 30 minutes after application of the system, and will be maintained for 30 minutes after its removal.

†After 24 hours, system is removed and a new one is applied to another site. Renewal of the system does not result in any significant alteration in the plasma levels, as long as the change is made without delay.

CIBA

For full details, please see the prescribing information on the next page.

Transderm®-Nitro nitroglycerin

Once-a-day, 24-hour protection against angina attacks

System can be applied anywhere except distal extremities. Doesn't compromise daily activities.

Transderm®-Nitro
(nitroglycerin)
Transdermal Therapeutic System

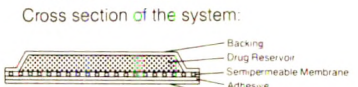
DESCRIPTION

Transderm-Nitro (nitroglycerin) transdermal therapeutic system is a flat unit designed to provide controlled release of nitroglycerin through a semipermeable membrane continuously for 24 hours following application to intact skin. Nitroglycerin (glyceryl trinitrate) is a prompt-acting vasodilator for the relief and prevention of anginal attacks. Systems are rated to release *in vivo* 5 and 10 mg nitroglycerin over 24 hours and are in sizes of 10 and 20 cm^2 respectively.

One-fifth of the total nitroglycerin in the system is delivered transdermally to the patient over 24 hours; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. The rated release of drug is dependent upon the area of the system; 0.5 mg nitroglycerin is delivered *in vivo* for every cm^2 of system size.

The Transderm-Nitro system comprises four layers as shown below. Proceeding from the visible surface toward the surface attached to the skin, these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid; 3) an ethylene/vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Cross section of the system:



ACTIONS

When the Transderm-Nitro system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In clinical studies transdermal absorption of nitroglycerin from a nitroglycerin system occurred in a continuous and well-controlled manner, for a minimum of 24 hours. Therapeutic effect can be anticipated 30 minutes after application of the system and to be maintained for 30 minutes after its removal.

INDICATIONS AND USAGE

Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS

Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS

In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS

Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS

Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION

Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response.

The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension, especially during orthostasis, indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.

Do not store above 86°F (30°C).

PATIENT INSTRUCTIONS FOR APPLICATIONS

A patient leaflet is supplied with the systems.

HOW SUPPLIED

Transderm-Nitro System Rated Release *in vivo*	Total Nitroglycerin in System	System Size	Carton Size
5 mg/24 hr	25 mg	10 cm^2	30 Systems (NDC 0083-2105-26)
5 mg/24 hr	25 mg	10 cm^2	7 Systems (NDC 0083-2105-07)
10 mg/24 hr	50 mg	20 cm^2	30 Systems (NDC 0083-2110-26)

C82-16 (3.82)

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Impaired Collateral Blood Flow Reserve Early After Nontransmural Myocardial Infarction in Conscious Dogs

RANDOLPH E. PATTERSON, MD, BEVERLY A. JONES-COLLINS, MD, and ROGER AAMODT, PhD

The purpose of this study was to determine the adequacy of collateral blood flow reserve of surviving myocardium 3 to 4 days after coronary occlusion in dogs. The proximal circumflex coronary artery was occluded in 9 conscious dogs, and in 7 of these the mid-left anterior descending coronary artery was also occluded. Three to 4 days after myocardial infarction, studies were performed under control conditions and during right ventricular pacing at the maximal heart rate that did not decrease aortic pressure.

Pacing increased the heart rate from 110 to 222 beats/min, caused no change in mean aortic pressure (112 to 118 mm Hg), and increased left atrial pressure marginally (13.5 to 16.0 mm Hg) ($0.05 < p < 0.10$). The ischemic zone mass that was dependent on collateral flow because of coronary occlusion was 56% (range 29 to 69) of the mass of the left ventricle, and the mass of the infarct occupied 21% (range 4 to 41) of the mass of the left ventricle. Subendocardial and mid-myocardial ischemic zone samples contained infarcted tissue and had low control values of coronary vascular conductance (flow/100 mm Hg mean aortic pressure) which tended to decrease during pacing: subendocardium, 0.18 to 0.02 ml·min^{-1}·g^{-1}/100 mm Hg ($0.05 < p < 0.11$), and mid-myocardium, 0.38 to 0.11 ($p < 0.05$). Coronary vascular conductance in normal zone subepicardium increased 35% from control conditions to pacing (1.24 to 1.69 ml·min^{-1}·g^{-1}/100 mm Hg; $p < 0.03$). In contrast, coronary vascular conductance in surviving myocardium located in the subepicardial layer of the ischemic zone did not change during pacing (1.17 to 1.21 ml·min^{-1}·g^{-1}/100 mm Hg).

It is concluded that collateral blood flow in surviving myocardium within the initial zone of ischemia returns to normal under control conditions by 3 to 4 days after coronary occlusion, but there is no reserve capacity to increase collateral conductance. Impaired collateral reserve in this unique canine model is probably related to multivessel occlusion and to the short period of time collateral vessels had to develop (3 to 4 days after coronary occlusion). If these findings are clinically applicable, they suggest that severe stress after acute myocardial infarction has the potential to provoke ischemia and its consequences in the surviving tissue supplied by occluded coronary arteries.

Gradual coronary occlusion over days to weeks in the dog usually does not cause myocardial infarction and leads to a substantial increase in coronary collateral function so that myocardial blood flow approaches normal values at rest.[1–3] After gradual coronary occlusion, collateral flow reserve during stress has been reported to be either normal[4] or slightly subnormal[5–7] during stress in dogs.

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In contrast to the gradual occlusion in the aforementioned studies, sudden coronary occlusion regularly causes myocardial infarction. A few hours to days after infarction, transmural mean blood flow to collateral-dependent myocardium is subnormal under resting conditions,[8–10] and the limited collateral flow that is available is redistributed from necrotic to surviving tissue.[8] This results in near-normal myocardial blood flow at rest in surviving tissue, an adaptation that might be expected to limit the development of additional ischemia. However, assessment of the reserve capacity to augment collateral myocardial blood flow is required to clarify the potential susceptibility of surviving myocardium to develop ischemia during stress.

Relatively little is known about collateral blood flow reserve after myocardial infarction. Recently, Hess and Bache[11] studied dogs 2 weeks after sudden occlusion of a single coronary artery. They found collateral myocardial blood flow during submaximal treadmill exercise to be 80% of normal in the tissue that contained minimal (1 to 25%) necrotic tissue, whereas flow was only 11% of normal in tissue that contained 75 to 100% necrotic tissue. These data indicate good collateral flow reserve during exercise in tissue with little or no necrosis 2 weeks after single vessel coronary occlusion.

The aforementioned study[11] was not designed to assess collateral flow reserve either early after myocardial infarction or in the presence of multivessel coronary disease. Because complications occur more frequently in patients in the first days after infarction[12] and in patients with multivessel coronary disease,[13] the purpose of the present study was to assess collateral blood flow reserve 3 to 4 days after myocardial infarction in dogs with occlusion of 2 coronary arteries. We also assessed factors that might influence collateral flow and its response to stress. The experimental model of 2 vessel coronary occlusion used in the present study was extremely difficult because of the high death rate, but it may offer some unique features with potential relevance to human acute myocardial infarction.

Methods

Experimental preparation: We anesthetized 41 foxhound dogs with sodium amytal, nitrous oxide, and halothane. Under sterile conditions, a thoracotomy was performed in the fourth left intercostal space and a polyethylene catheter was placed into the left internal mammary artery. We next opened the pericardium and dissected the left circumflex coronary artery near its origin (before any major ventricular branches), and the left anterior descending coronary artery in its mid-portion (after the second or third left ventricular branches). A deflated balloon occluder (Brunswick Manufacturing, Quincy, Massachusetts) was positioned around the circumflex coronary artery and snares (1-0 silk inside a plastic catheter) were placed around both coronary arterial branches. Great care was taken to anchor the balloon and snare occlusive devices so that they would not cause coronary occlusion until the desired time. A polyethylene catheter was then inserted through a stab wound in the left atrial appendage and secured in the left atrium. Finally, a 3-pronged electrode plate was secured by sutures on the epicardial surface of the outflow tract of the right ventricle. The connectors from all of the implanted instruments were tunneled under the skin to a subcutaneous pouch at the base of the neck. The catheters were filled with heparin, 1,000 U/ml, sealed by a knot and a heat-seal at the tip, and the chest was closed in layers. The dogs were trained to lie on their right side in a quiet, dimly lit room during the period of recovery from surgery.

Protocol: After recovery from surgery for 1 to 3 weeks, each dog received morphine, 1 mg/kg, and local anesthesia with lidocaine to exteriorize the connectors from the subcutaneous pouch. The catheters were connected to Statham P23Db transducers to measure continually aortic and left atrial pressure, along with an electrocardiogram on a Sanborn model 350 physiologic recorder. Each dog received lidocaine, 1 mg/kg, as an intravenous bolus and a 2 to 3 mg/min continuous infusion before inflation of the pneumatic occluder on the circumflex coronary artery. The occluder was inflated with saline solution to one fourth of the volume that had been required at the time of surgery to cause coronary occlusion. Every 15 minutes an additional one fourth of this volume was injected into the occluder until the circumflex coronary artery was totally occluded (45 minutes after the beginning of balloon inflation). The circumflex artery snare was pulled and secured to ensure total permanent occlusion as soon as the last volume

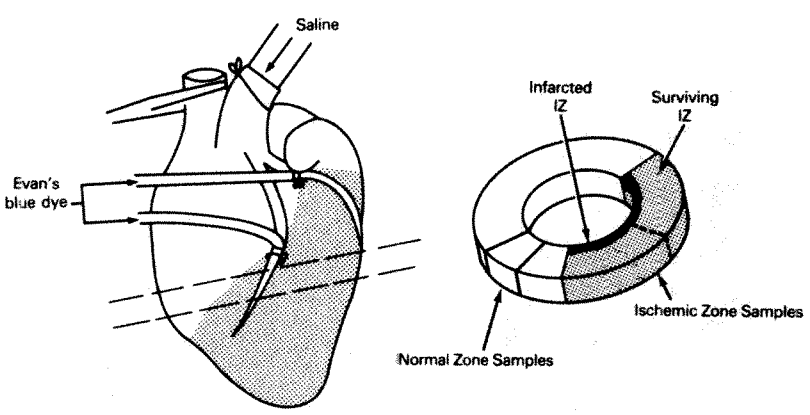

FIGURE 1. Diagram of postmortem methods to identify ischemic zone and myocardial infarction. **Left,** diagram of a dog heart showing how the circumflex and left anterior descending coronary arteries were perfused by cannulas inserted distal to the points of occlusion. These arteries were perfused with Evans blue dye at the same pressure as the other unoccluded coronary arteries, which were perfused with fluorosine through the aortic root. The left ventricle was cut into 4 to 5 mm thick doughnut-shaped slices, one of which is shown in the diagram **at the right.** The blue-stained ischemic zone was marked on both sides of each slice by a careful incision at the border between blue and fluorosine dye, and each slice was incubated in triphenyl tetrazolium to stain the surviving tissue red. Each slice was photographed on both sides for integration of areas of the normal, ischemic (IZ), and myocardial infarction zones. The average area of normal zone, ischemic zone, and myocardial infarction, for both sides of each slice was multiplied by the weight of each slice to give the total mass of normal, ischemic, and myocardial infarction zones for the entire ventricle. Samples were dissected from normal and ischemic zones, as shown, to count microsphere radioactivity for myocardial blood flow. Ischemic zone samples were at least 10 mm inside the blue-stained border to avoid normal zone contamination, and samples were divided into transmural thirds from subendocardium, mid-myocardium, and subepicardium.

of saline solution had been injected into the balloon. Five minutes after circumflex artery occlusion, we pulled and secured the left anterior descending snare in all dogs in which mean left atrial pressure had not increased above 15 mm Hg. The dogs were monitored and received lidocaine for 3 to 5 hours after coronary occlusion. We began coronary occlusion on 41 dogs, and 27 died within the first day after occlusion. Thus 14 dogs survived 3 to 4 days. The pacemaker electrodes did not work in 2 of these dogs, and 2 died from ventricular fibrillation during right ventricular pacing (200 to 240/min). One dog did not receive radionuclide-labeled microspheres because of left atrial catheter failure, so 9 dogs were studied. Of these 9 dogs, 7 had 2 vessels occluded, and 2 had circumflex artery occlusion alone because left atrial pressure had been over 15 mm Hg 5 minutes after circumflex artery occlusion.

Myocardial blood flow measurements: These 9 dogs received morphine, 1 mg/kg, 3 to 4 days after coronary occlusion, and their catheters and right ventricular pacing wires were exteriorized. Thirty minutes after beginning continuous electrocardiographic and pressure monitoring we injected 2 million 15 μm diameter microspheres labeled with one of the following radionuclides: iodine-125, cerium-141, chromium-51, strontium-85, niobium-95, or scandium-46 (3M, St. Paul, Minnesota). A reference sample of aortic blood was withdrawn at 15.2 ml/min beginning before and continuing for 90 seconds after microsphere injection. The reference blood sample was not collected adequately during either the control or pacing period in 4 dogs. Criteria for inadequate collection were failure to turn on the aortic blood withdrawal pump before microsphere injection (n = 2) and having the blood withdrawal stop within the first 60 seconds after microsphere injection because of clotting in the aortic catheter (n = 2). Thus, in these dogs only relative blood flow to different regions of the heart (ischemic zone versus normal zone) could be measured. This ratio of blood flows is useful because it relates the blood supply to the ischemic region to the normal region where patent coronary arteries allow autoregulation to match blood supply to metabolic demands.[1,2] Two of these 4 dogs were the dogs with single vessel occlusion. After the control measurements, we paced each dog's right ventricle to 200/min and increased pacing by 20/min every 15 to 30 seconds until there was a decreasing mean aortic pressure. We waited 15 minutes and resumed pacing at 20/min slower than the maximum. After 2 minutes of pacing, we measured pressures and injected microspheres labeled with a different radionuclide. Pacing was continued 1 to 2 minutes after microsphere injection to allow microspheres to distribute to tissues. The dogs were euthanized with an overdose of pentobarbital.

Postmortem analyses: We cannulated each occluded coronary artery distal to the site of its occusion and the aorta 1 to 2 cm above the coronary ostia (Fig. 1). The dye reservoirs were positioned high above the heart to perfuse the coronary arteries at the same pressure as the aorta (100 mm Hg), delivering fluorosine into the aorta and Evans blue dye into the coronary arteries distal to their sites of occlusion.[14] Thus, the regions supplied by the occluded arteries and therefore dependent on collateral flow and potentially ischemic, were identified by blue stain. Myocardium supplied by patent arteries was identified by the fluorosine stain. After removing the atria and right ventricle, we cut each heart into 8 to 10 doughnut-shaped slices, 4 to 5 mm thick, from apex to base (Fig. 1). Each slice was carefully dissected to make an incision along the irregularly shaped boundary between blue and fluorosine stains on both sides of each slice. We incubated each slice in triphenyl tetrazolium for 1 hour at 37°C to stain noninfarcted tissue red. The heart slices were preserved in 10% buffered formalin for 24 hours and then each side was individually photographed. The photographic slides were projected to trace the outlines of the total left ventricular slice, potentially ischemic zone (marked by previous incisions), and the tetrazolium-negative region of myocardial infarction (Fig. 1). The areas of each region were integrated for each side of the heart slice, averaged, and multiplied by the weight of each slice to yield the masses (g) of the left ventricular slice, ischemic zone, and myocardial infarction region for each slice. The total masses of each region were summed for all slices to yield the total masses of the left ventricular ischemic zone and myocardial infarction.

Finally, we dissected samples from the normal zone remote from the ischemic zone, and from the center of the circumflex-dependent ischemic zone at least 1 cm inside the incision that marked the boundary between the ischemic and normal zones. These samples for microsphere radioactivity counting were divided into subendocardial, mid-myocardial, and subepicardial layers. The samples were weighed and counted in appropriate energy windows. Counts were corrected for crossover activity from other radionuclides by a decontamination matrix of simultaneous linear equations, as previously described.[15] Myocardial blood flow was calculated by the following formula: (tissue counts)·(sample weight)$^{-1}$·(refer-

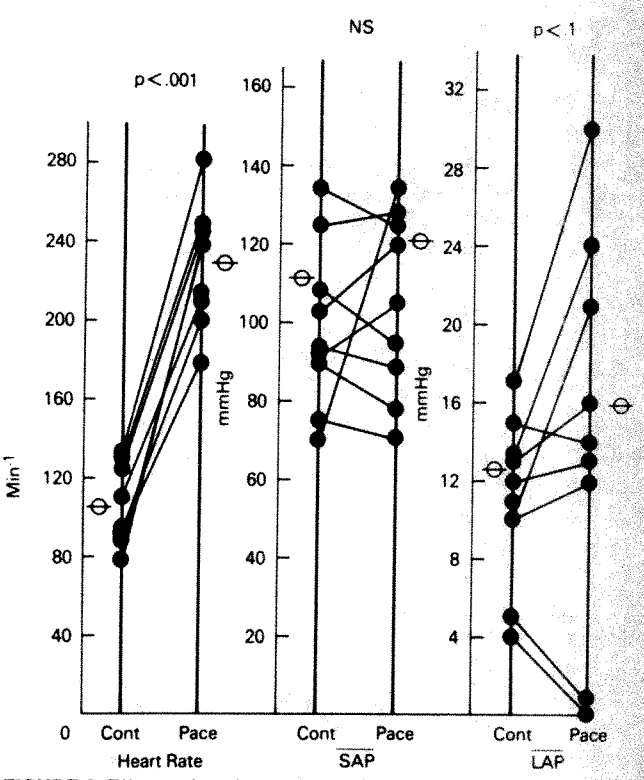

FIGURE 2. Effects of pacing-tachycardia on systemic hemodynamics 3 to 4 days after myocardial infarction. These 3 graphs show values for heart rate (beats·min^{-1}), mean aortic or systemic arterial pressure ($\overline{SAP}$, mm Hg), and mean left atrial pressure ($\overline{LAP}$, mm Hg). Data for the same dog are shown by **closed circles** and connected by **lines** from the control (Cont) value on the **left** to the value during pacing (Pace) on the **right** in each of the 3 graphs. The mean values of each variable during each condition are shown by the **open circles** beside each **bar.** The p values shown above each graph resulted from paired Student's *t* tests (n = 9).

ence blood sample counts)$^{-1}$·(rate of withdrawal of the reference blood sample).[16] Because the major focus of the present study was on the measurements made a few minutes before the animals' death, we did not attempt to calculate microsphere loss in these studies.[15]

Data analysis: We tested the significance of changes in variables between control and pacing periods by Students' *t* test for paired data. The best fit equation (least squares linear regression) was calculated, as was the correlation coefficient (*r*).[17] P values less than 0.05 were considered significant, and p values less than 0.1 but greater than 0.05 were reported as marginally significant.

Results

Sizes of ischemic and infarct zones: The mass of the ischemic zone averaged 56% of the left ventricle (range 38 to 69), the mass of the myocardial infarction averaged 21% of the left ventricle (range 4 to 41), and the mass of the infarct averaged 32% of the ischemic zone (range 7 to 74). Gross examination of specimens stained by tetrazolium before microsphere counting revealed some myocardial infarction in all samples from the subendocardium and in some samples from the mid-myocardium, but in no samples from the subepicardium.

Hemodynamics: Figure 2 shows heart rate, mean aortic pressure, and left atrial pressure during control and pacing periods 3 to 4 days after myocardial infarction. Right ventricular pacing increased the heart rate twofold, caused no change in mean aortic pressure, and caused a marginal increase in left atrial pressure ($0.05 < p < 0.1$).

Myocardial blood flow: The average transmural myocardial blood flow to the normal zone was 1.67 ml·min^{-1}·g^{-1} during control conditions and increased to 2.21 during pacing (n = 5). Mean transmural blood flow to the ischemic zone was reduced 3 to 4 days after infarction ($p < 0.05$), and did not change during pacing (0.54 to 0.49 ml·min^{-1}·g^{-1}). Because some dogs showed changes in aortic pressure, we calculated coronary vascular conductance (myocardial blood flow per 100 mm Hg mean aortic pressure). Pacing in the 5 dogs with all microsphere blood samples available increased mean transmural vascular conductance to the normal zone (Fig. 3, top) ($p < 0.03$), whereas mean transmural collateral conductance to the ischemic zone was lower at rest and did not change during pacing (Fig. 3, bottom). When each transmural layer was analyzed individually, the subendocardial and mid-myocardial collateral vascular conductances were low at rest and tended to decrease further during right ventricular pacing ($p < 0.11$ and $p < 0.05$, respectively). Collateral vascular conductance to the subepicardial layer of the normal zone increased during pacing from 1.21 to 1.61 ml·min^{-1}·g^{-1}/100 mm Hg ($p < 0.05$). In contrast, vascular conductance to the surviving subepicardial layer of the ischemic zone was normal at rest and did not increase during pacing stress (1.17 to 1.21 ml·min^{-1}·g^{-1}/100 mm Hg).

Relation of collateral flow reserve to hemodynamics and extent of infarction: We analyzed the potential influence of several factors on collateral flow and its reserve capacity to increase during pacing stress, 3 to 4 days after infarction. The fraction of the ischemic zone that developed myocardial infarction correlated closely with resting subendocardial flow ($r = 0.87$), but not with resting subepicardial flow ($r = 0.43$) (Fig. 4). These correlations indicate that 3 to 4 days after infarction collateral blood flow in the infarcted subendocardium is related closely to the extent of infarction. In contrast, collateral blood flow to the surviving subepicardial layer is nearly normal and relatively independent of the extent of infarction. Pacing tends to decrease the relative distribution of flow to the ischemic zone for any given extent of infarction, although the correlations between flow (ischemic zone/normal zone)

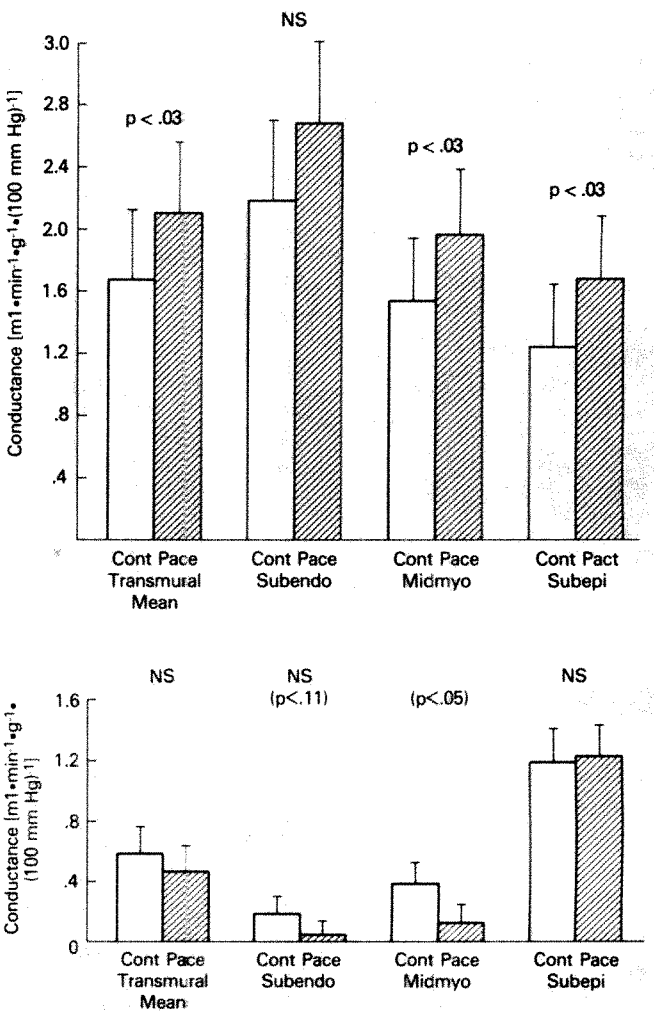

FIGURE 3. Effects of pacing-tachycardia on coronary vascular conductance 3 to 4 days after myocardial infarction. **Top,** data for the normal zone and **bottom,** data for the ischemic zone. Coronary vascular conductance was calculated as myocardial blood flow divided by mean aortic pressure, (ml·min^{-1}·g^{-1}/100 mm Hg). Data are shown for the following samples: transmural mean, subendocardial (subendo), midmyocardial (midmyo), and subepicardial (subepi). The **clear bars** show the control (Cont) values and the **shaded bars** the values during pacing (Pace). The p values resulted from paired Student's *t* tests. The brackets show 1 standard error of the difference (n = 5 because of problems with collecting reference arterial blood samples in 4 of 9 dogs).

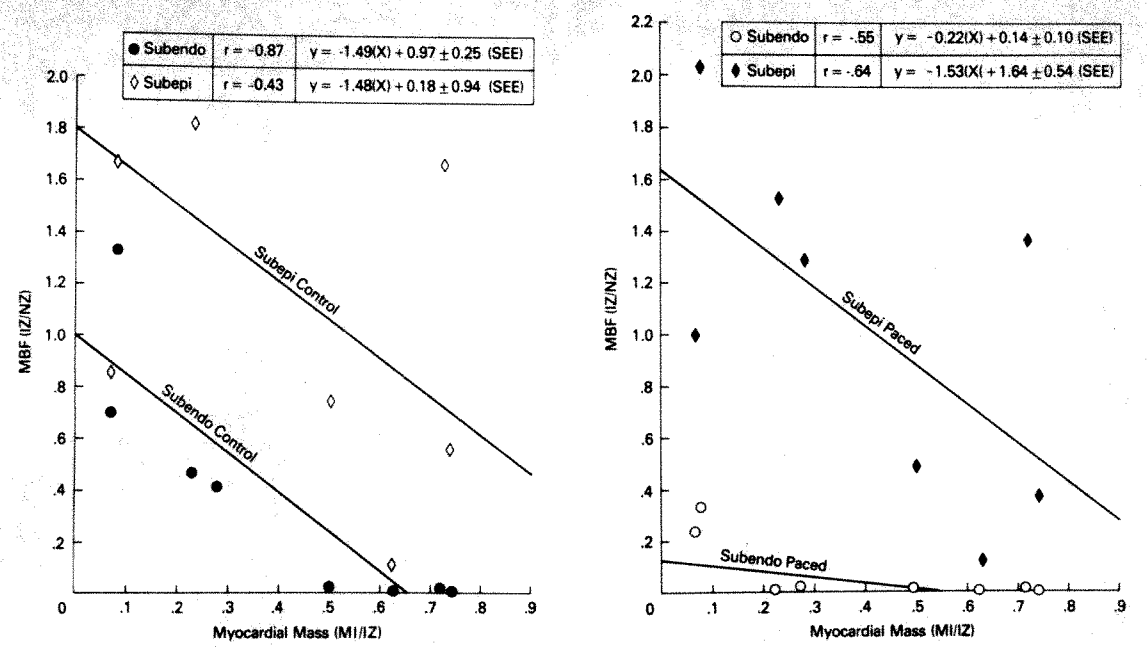

FIGURE 4. Relations between the myocardial blood flow (MBF) ratio, ischemic zone/normal zone (IZ/NZ), and the fraction of the ischemic zone that is infarcted (MI/IZ) 3 to 4 days after infarction. **Left,** during control conditions, and **right,** during pacing-tachycardia (n = 9). **Left,** the **closed circles** represent data for the subendocardium, and the **open circles,** diamond-shaped symbols for the subepicardium. The **boxed area** shows the correlation coefficients (*r*) and equations for the linear regression lines, ± the standard error of the estimate (SEE). **Right,** the symbols are shown in **the box.** Note that the best correlation between blood flow (IZ/NZ) and the fraction of the ischemic zone that undergoes infarction (MI/IZ) is found for the subendocardium under control conditions ($r = -0.87$). Subepicardial samples (which had no gross evidence of infarction) have more blood flow for any given percent infarction during control or pacing conditions (n = 9).

and size of myocardial infarction (myocardial infarction mass/ischemic zone mass) are not strong ($r = -0.55$ for subendocardium and $r = 0.64$ for subepicardium).

Figure 5 shows a fair correlation between collateral flow 5 minutes after coronary occlusion versus 3 to 4 days after occlusion during pacing ($r = 0.73$), suggesting that collateral flow reserve 3 to 4 days after myocardial infarction depends in part on preexisting collateral flow. The initial collateral flow 5 minutes after coronary occlusion does not permit quantitative prediction of collateral flow reserve 3 to 4 days after acute myocardial infarction. Figure 6 shows the lack of relation between the left atrial pressure and subepicardial collateral flow during control ($r = 0.44$) and pacing ($r = 0.29$).

Discussion

The major objective of the present study was to determine whether the coronary vascular conductance to surviving myocardium has the reserve capacity to increase during pacing tachycardia 3 to 4 days after acute myocardial infarction. We also examined factors that might influence collateral flow reserve 3 to 4 days after infarction. The design of the present study differs from most previous reports in that the dogs had myocardial infarction before collateral blood flow reserve was tested. Most physiologic studies of coronary collateral function have been designed to avoid myocardial infarction.[8] Collateral reserve after myocardial infarction and multivessel coronary occlusion was studied because inadequate collateral blood flow reserve in surviving myocardium might predispose the heart to further ischemia and infarct extension after the initial acute myocardial infarction. This relation might be expected because myocardial infarction size has been found related to the collateral myocardial blood flow available a few minutes after coronary occlusion.[8–10,18]

One previous study by Hess and Bache[11] found only a moderate reduction in collateral blood flow to regions with minimal myocardial infarction during exercise in dogs 2 weeks after acute occlusion of a single coronary vessel. The present study design differed from the previous study in 2 major ways: Collateral blood flow reserve was assessed earlier (3 to 4 days) after acute coronary occlusion, and 2 major coronary vessels were occluded in 7 of the 9 animals studied. The experimental model of multivessel coronary disease 3 to 4 days after myocardial infarction seems relevant to the patients in whom complications of myocardial infarction are most likely to develop in the clinical situation,[12,13] but the exceedingly high death rate of these dogs limits the number of animals that can realistically be entered into a study.

Coronary vascular conductance at rest and during pacing tachycardia: The results of the present investigation indicate that coronary vascular conductance at rest in collateral-dependent myocardium 3 to 4 days after acute coronary occlusion is reduced in subendocardial and mid-myocardial layers. These regions contain grossly visible infarcted tissue. Pacing stress led to a further decrease in vascular conductance in these deep layers. In contrast, collateral conductance at rest returned to values equal to that in the normal

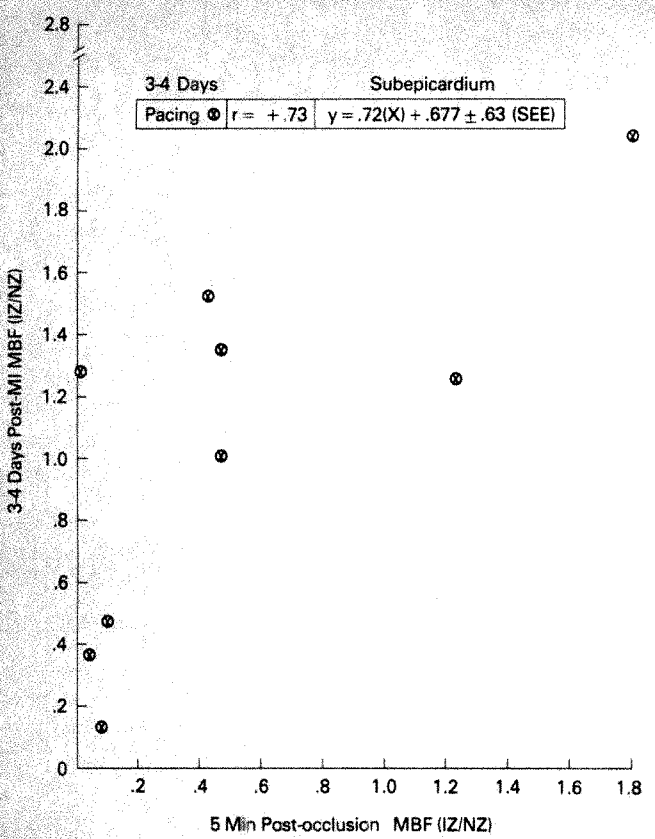

FIGURE 5. Relation between the myocardial blood flow (MBF) ratio, ischemic zone/normal zone (IZ/NZ) in the noninfarcted subepicardium 5 minutes after coronary occlusion versus 3 to 4 days later, after myocardial infarction, during pacing-tachycardia . Other symbols and abbreviations as in Figure 4 (n = 9). Note that the index of collateral blood flow reserve (IZ/NZ during pacing) 3 to 4 days after myocardial infarction correlates moderately well with the initial collateral blood flow available 5 minutes after coronary occlusion ($r = 0.73$). The initial collateral flow ratio does not allow quantitative prediction of subsequent collateral flow reserve.

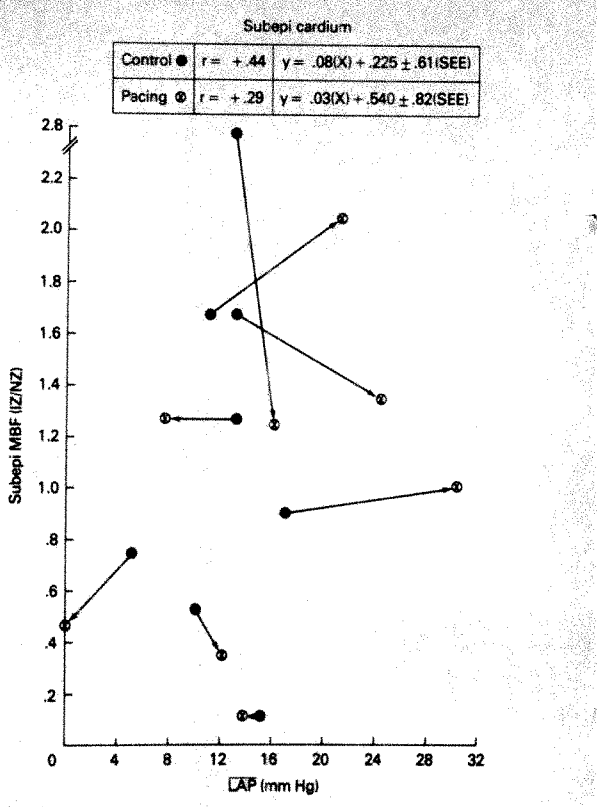

FIGURE 6. Relation between the myocardial blood flow ratio (ischemic zone/normal zone) and mean left atrial pressure during control (**closed circles**) versus pacing (**x inside circles**) conditions, 3 to 4 days after infarction. Note that there is no particular relation between the changes in blood flow and left atrial pressure during either control or pacing periods, 3 to 4 days after infarction. Other symbols and abbreviations as in Figures 4 and 5 (n = 9).

zone in the subepicardial layers. Nonetheless, vascular conductance did not increase in the surviving collateral-dependent subepicardial layers during pacing to the same extent that it did in normal myocardium that lay outside the collateral-dependent zone. The potential functional significance of this finding will be discussed after a critique of our methods.

Methodology: Several methodologic considerations are important to consider. First, dogs were studied in the awake state to avoid the effects of anesthesia and acute surgical trauma. Second, we defined the presence or absence of myocardial infarction by examination of both surfaces of heart slices 4 to 5 mm thick after staining with triphenyl tetrazolium. The ability of this staining technique to distinguish necrotic from surviving tissue within the vascular distribution of the occluded coronary artery has been validated in this laboratory by histopathologic examination.[14] Some myocardial infarction was found in all of the subendocardial samples and most mid-myocardial samples that were used for microsphere measurements of blood flow. In contrast, none of the subepicardial samples manifested any evidence of infarction. Although large regions of myocardial infarction could be excluded by the method employed, it is possible that a small amount of necrotic tissue existed in the subepicardial samples. Even if these samples contained up to 10% necrotic tissue with zero blood flow, this would cause our microsphere blood flow measurements to underestimate true collateral myocardial blood flow by only 10%. Thus, it is unlikely that our conclusion that subepicardial collateral vascular conductance does not increase normally 3 to 4 days after myocardial infarction is due to an artifact resulting from the presence of necrotic tissue in the samples.

Third, if the samples of supposedly ischemic myocardium used for collateral flow measurements had included some overlapping tissue dependent on an unoccluded coronary artery, then our measurement of apparent collateral blood flow might be increased artifactually. This artifactual increase in collateral myocardial blood flow is most serious during interventions that increase blood flow through normally patent coronary arteries.[19] In the present study we minimized the likelihood of this artifact influencing our results by injecting dye into the coronary arteries distal to their sites of occlusion and dissecting samples from at least 10 mm inside the dye-stained border. In other studies using

similar dye injection methods and a microsphere technique to label tissue supplied by normally patent arteries, the overlapping normal tissue was located primarily in the subendocardium[20] and was less than 5 mm from the lateral border of the dye-stained zone.[8,20,21] Further, the increase in normal zone blood flow in the present study were not large enough to cause a large artifactual increase in apparent collateral blood flow. These considerations indicate that no significant contribution to subepicardial collateral blood flow would be expected from overlapping normal zone tissue in the present study.

Fourth, right ventricular pacing does not stimulate a maximal increase in coronary blood flow. Studies in man[22] and dog[7] have indicated that exercise causes a greater increase in coronary blood flow than does pacing to the same heart rate. However, after adjusting the increase in coronary blood flow for the increased aortic pressure during exercise, exercise appears to cause only a 30 to 50% greater increase in coronary vascular conductance than does pacing to the same heart rate.[7,22] Thus, the failure of collateral blood flow to increase in surviving subepicardial tissue during pacing does not appear to be an artifact of an inadequate stimulus to collateral blood flow. The tachycardia-stress employed in the present study is a stress that frequently occurs in patients with tachyarrhythmias 3 to 4 days after myocardial infarction.[12]

Fifth, pacing was performed for 2 minutes before and 1 to 2 minutes after microsphere injection to ensure tissue distribution. No major hemodynamic changes were noted during pacing probably because the rate had been selected from previous tests in the same dog to ensure stable mean arterial pressure. Left atrial pressure increased in 4 dogs by more than 3 mm Hg, decreased by 3 mm Hg in 2 dogs, and did not change in 3 dogs (Fig. 2). Changes in left atrial pressure were not related to changes in heart rate, aortic pressure, collateral myocardial blood flow (Fig. 6), or myocardial infarction size.

Sixth, the present study measured blood flow reserve in collateral-dependent myocardium 3 to 4 days after acute myocardial infarction, but we did not measure an index of ischemic injury during pacing stress. Thus, the conclusions are related specifically to collateral blood flow reserve—a major determinant of the potential for ischemia—rather than to the severity of ischemia itself. We did express collateral blood flow reserve as a fraction of the flow reserve measured simultaneously in the regions of the left ventricle supplied by patent coronary arteries. These normal regions of the heart should show autoregulatory changes in blood flow to reflect the level of myocardial oxygen demand at the time of collateral blood flow measurements.[4]

Mechanisms influencing collateral flow: Several mechanisms probably contribute to limited collateral myocardial blood flow reserve after myocardial infarction. *First, occlusion near the origin of the circumflex and the mid-portion of the left anterior descending coronary arteries rendered 56% of the left ventricle ischemic in the present study.* Occlusion of 2 of 3 vessels deprives the heart of 1 of its 2 potential sources of collateral vessels that would be available after single vessel occlusion. This effect contributes to the observation that collateral myocardial blood flow decreases as a larger fraction of the left ventricle is rendered ischemic by coronary occlusion.[23,24] Multivessel occlusion in 7 of 9 dogs in the present study must have contributed to the fact that we observed lower collateral flow reserve than have others.[11] Also, the dogs' individual variability in collateral development probably influences collateral flow reserve 3 to 4 days after infarction. This is suggested by Figure 5, which indicates a reasonable correlation between collateral flow reserve 3 to 4 days after infarction and the initial collateral flow 5 minutes after coronary occlusion ($r = 0.73$).

Second, 3 to 4 days after acute coronary occlusion the coronary collateral vessels would be in only an early stage of their growth transformation process, which usually takes 4 to 6 months.[2,7] The early days of collateral development appear to be associated with less flow reserve than is found later.[2–7] Thus, the brief time available for collateral development undoubtedly contributed to the more severe impairment of subepicardial blood flow reserve observed in the present study compared with the moderate impairment reported by others 2 weeks after acute occlusion.[11]

Third, the 9 dogs studied were selected from 14 survivors of multivessel occlusion. Most of the 41 dogs subjected to these coronary occlusions in the awake, sedated state died within a few hours. The relatively high blood flow to normal zone myocardium after occlusion of 2 coronary arteries probably reflects reflex stimulation of the heart to maintain the circulation after the large myocardial infarction. Thus, the surviving dogs selected for study may differ from the general population of dogs in ways that could influence their subepicardial blood flow reserve measured after infarction. It seems most likely that the selection process would have favored dogs with better collateral flow reserve, again making our results conservative in estimating the severity of the flow deficit.

Fourth, impaired collateral flow reserve in the surviving subepicardium may be explained in part by the decreased diastolic time per minute during pacing, because collateral coronary flow occurs primarily during diastole.[25,26] The level of left atrial pressure during pacing (16 mm Hg) did not appear to inhibit subepicardial collateral flow, as indicated by the poor correlations between left atrial pressure and its changes and subepicardial collateral flow (ischemic zone/normal zone, $r = 0.29$ during pacing). This lack of effect of left ventricular filling pressure on subepicardial collateral flow reserve is not surprising because left ventricular diastolic pressure exerts its major inhibitory effect on collateral blood flow in the subendocardium.[27–30]

Clinical implications: The validity of extrapolating from animal studies to human disease is always uncertain. Man may have less potential for collateral vessel development than does the dog, which suggests that the present animal study may be conservative in that it estimates better coronary collateral flow than is present

in patients 3 to 4 days after acute myocardial infarction.[31] It is likely that there is overlap between the status of collateral flow development in individual patients and animals. If this is so, then the results of this study suggest that some patients with multivessel coronary disease have inadequate collateral blood flow reserve capacity 3 to 4 days after myocardial infarction.

The present study should not be interpreted as evidence that early mobilization of patients with an uncomplicated clinical course after acute myocardial infarction is necessarily dangerous. Rather, these data in animals support a "common sense approach" to early mobilization.[32] If early mobilization caused a large increase in heart rate, most cardiologists would advise a decrease in the level of physical activity.[33] Further clinical data suggest the feasibility of discharging carefully selected patients 1 week after myocardial infarction[34] or of treadmill stress testing 2 to 4 weeks after myocardial infarction.[35,36] These clinical practices have been restricted to carefully selected subgroups of patients,[32–36] who probably differ from these animals with multivessel disease 3 to 4 days after a large myocardial infarction. Further, the demonstration of impaired collateral flow reserve in the present study may be relevant to the mechanism of positive stress tests after acute myocardial infarction.[35,36]

Acknowledgment

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Relation Between Regional Distribution of Thallium-201 and Myocardial Blood Flow in Normal, Acutely Ischemic, and Infarcted Myocardium

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Myocardial localization of thallium-201 was compared with direct measurements of myocardial perfusion in normal, acutely ischemic, and recently infarcted myocardium. Studies were performed in 6 chronically instrumented dogs that were subjected to myocardial infarction by occlusion of the proximal left circumflex coronary artery. Four days after myocardial infarction, thallium-201 and 9 ± 1 μm niobium-95-labelled microspheres were injected simultaneously after acute left anterior descending coronary arterial occlusion; the animals were killed 5 minutes later and the entire left ventricle was sectioned into 1 to 2 g samples. Regression analyses between thallium-201 activity and regional myocardial blood flow using all myocardial samples demonstrated a very close linear relation in each dog; *r* values were 0.98 or greater, indicating that the initial localization of thallium-201 in acutely ischemic and recently infarcted myocardium as a function of regional blood flow was essentially identical. Consequently, in each dog the regional distribution of thallium-201 closely approximated myocardial perfusion over a wide range of blood flow and potentially different local metabolic conditions that may be encountered in the clinical use of the isotope.

Thallium-201, a biologically active ion, is the most commonly used tracer isotope for evaluating regional myocardial perfusion. Thallium-201 scintigraphy is used to assess transient myocardial ischemia induced by exercise stress[1–3]; evaluation is commonly required in the presence as well as absence of prior myocardial infarction. Thallium-201 scintigrams have been recorded serially after acute myocardial infarction as measurements of initial and subsequent dimensions of the ischemic zone (that is, a thallium-201 deficit that decreases on repeat scintigraphy has been interpreted as a decrease in the zone of initial ischemia and consequently salvage of ischemic myocardium).[4,5] Optimal assessment of baseline or serial changes, or both, in myocardial perfusion in these different pathologic situations requires that the myocardial localization of an imaging agent be principally determined by regional myocardial perfusion and not by perturbations in cellular metabolism which may vary with different conditions of reduced blood flow.

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The objective of the present study was to compare the myocardial localization of thallium-201 with direct measurements of myocardial perfusion by inert nondiffusable microspheres in normal, acutely ischemic, and recently infarcted myocardium. These interventions were selected to simulate the different conditions of reduced blood flow and potentially different local myocardial metabolic influences that may be encountered in the clinical use of this isotope.

Methods

Experimental preparation: Six mongrel dogs weighing 15 to 25 kg were anesthetized intravenously with thiamylal sodium, 30 to 40 mg/kg body weight, and ventilated with a respirator. A left thoractomy was performed in the fourth intercostal space. The circumflex coronary artery was dissected free just proximal to the first marginal branch, and the left anterior descending coronary artery was dissected free just distal to the first diagonal branch. An adjustable occluder was loosely positioned around each vessel and stabilized to the fibrous tissue adjacent to the vessel bed. Polyvinyl chloride catheters (outer diameter, 3 mm) were filled with heparin and inserted into the left atrium through the left atrial appendage and in the ascending aorta through the left internal thoracic artery. The occluders and catheters were tunneled to separate subcutaneous pouches at the base of the neck. The dogs were then allowed to recover from the surgical procedure.

Seven to 10 days after recovery from the surgical procedure, each dog was sedated with 0.3 to 0.4 mg/kg of morphine sulfate intramuscularly and the circumflex occluder was exteriorized from the subcutaneous pouch after lidocaine infiltration anesthesia. The circumflex coronary artery was per-

manently occluded. Lidocaine, 2 mg/kg, and morphine sulfate, 0.06 to 0.08 mg/kg, were administered intravenously to reduce arrhythmias and to minimize discomfort. The electrocardiogram was monitored before and after occlusion; proper function of the occluder was verified by elevation of S-T segments and an increase in heart rate after occlusion, and the presence of ventricular arrhythmias 24 hours after occlusion. The dogs were then allowed to recover from the occlusion.

Thallium-201 and microsphere injection: Three to 4 days after infarction, each dog was again sedated with 0.3 to 0.4 mg/kg of morphine sulfate intramuscularly. The pouches were infiltrated with lidocaine and the catheters and the left anterior descending occluder were exteriorized. Each dog was given lidocaine and morphine sulfate intravenously. Blood flow was measured using 9 ± 1 μm scandium[46]-labelled microspheres before occlusion to ensure that premature closure of the snare had not occurred and that acute ischemia was subsequently initiated. The left anterior descending coronary artery was then completely occluded. One minute after complete occlusion, thallium-201, 0.5 mCi, was injected into the left atrium; niobium[95]-labelled microspheres were injected into the left atrium immediately after the thallium-201 injection. Serial blood samples were withdrawn from the aortic catheter as previously described[6,7] for calculation of regional blood flow. The occlusion was maintained and 5 minutes after injection of thallium-201 each animal was anesthetized rapidly with 40 mg/kg of thiamylal sodium; the heart was fibrillated with potassium chloride solution and immediately extracted and cooled to approximately 5 to 10°C.

Tissue samples for comparing blood flow and thallium distribution: The heart was immediately prepared for sectioning. The right ventricle, atria, aorta, and pericardial fat were removed. The left ventricle was sectioned into 4 transverse layers of approximately equal thickness (Fig. 1); the apical ring was sectioned into 1 anterior and 1 or 2 posterior regions; the other rings were sectioned into anterior, anterior papillary, lateral, posterior papillary, posterior, and septal regions. Each apical region was further sectioned into 3 transmural layers of approximately equal thickness, whereas each of the other regions was sectioned into 4 transmural layers. This procedure generated approximately 80 tissue samples, weighing 0.7 to 2.0 g, for comparison of blood flow and thallium distribution. The samples were placed in scintillation vials containing formalin for subsequent histologic processing.

Thallium-201 activity in the tissue sample in each vial was counted with a gamma spectrometer with a 54-100 keV window. The tissue samples and reference blood samples were then recounted for niobium[95] and scandium[46] activity at optimal window settings. Background activity and spillover activity were corrected by an appropriate computer program. Flow to each myocardial region was calculated using the following standard formula: $Q_m = Q_r \times C_m/C_r$, where Q_m = myocardial blood flow (ml/min), Q_r = reference blood flow (ml/min), C_m = count activity in the myocardium, and C_r = count activity in the reference blood samples. Myocardial blood flow for each sample was expressed as ml/min per g. Thallium-201 activity was expressed as counts/min per g. The relation of regional myocardial blood flow and thallium-201 distribution was analyzed by linear regression analyses.

Histology: After measurement of tissue radioactivity, the samples were prepared for histologic sectioning as described previously.[7] Each tissue sample was sectioned serially with a microtome and 4 histologic sections were taken from different depths through each small sample and stained with hematoxylin and eosin. Myocardial infarction was defined as inflammatory cell infiltrate, loss of normal cell architecture, and cellular dissolution. The extent of infarcted myocardium in each sample was determined with planimetry of histologic infarction in each section using a projection microscope and ultrasonic graph pen.[7]

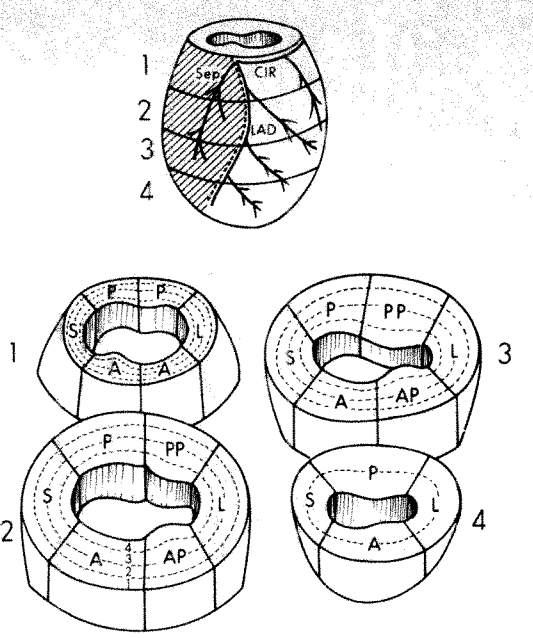

FIGURE 1. Diagram illustrating the technique for sectioning the left ventricle. The atrial tissue and right ventricle were removed as indicated by the **stippled** and **lined areas.** The left ventricle was sectioned into 4 transverse rings. Each ring was sectioned into circumferential regions: anterior (A), septal (S), posterior (P), posterior papillary (PP), lateral (L), and anterior papillary (AP). Each circumferential region in rings 1, 2, and 3 was divided into 4 equal epicardial and endocardial layers.

Results

Figure 2 illustrates the relation between the regional distribution of thallium-201 and myocardial blood flow as measured by 9 ± 1 μm microspheres. Data from all samples are plotted in each dog. In each dog there were myocardial regions in which blood flow was reduced less than 0.10 ml/min per g as a result of acute ischemia as well as of the infarction, initiated 3 days earlier. These data demonstrate a very close linear relation between thallium-201 localization and regional myocardial blood flow; *r* values were 0.98 or more in each dog. Thus the initial net localization of thallium-201 in acutely ischemic and recently infarcted myocardium as a function of regional blood flow was essentially identical. The *y* intercepts of each regression equation were slightly above zero. The slight scatter in data points was no greater at low as compared with normal flow ranges. The close linear relation and intercepts that approach zero indicate that net initial localization of thallium-201 closely approximates regional myocardial perfusion over a wide range of blood flow in acutely ischemic and recently infarcted myocardium. The differences in slopes resulted from differences in animal weights.

Proximal circumflex arterial occlusion resulted in an average infarct of 28.8% of the left ventricle (range 24 to 35%). The infarction extended to a variable degree of the epicardial surface. In the larger infarcts, infarction in the central ischemic regions extended to the epicardial surface.

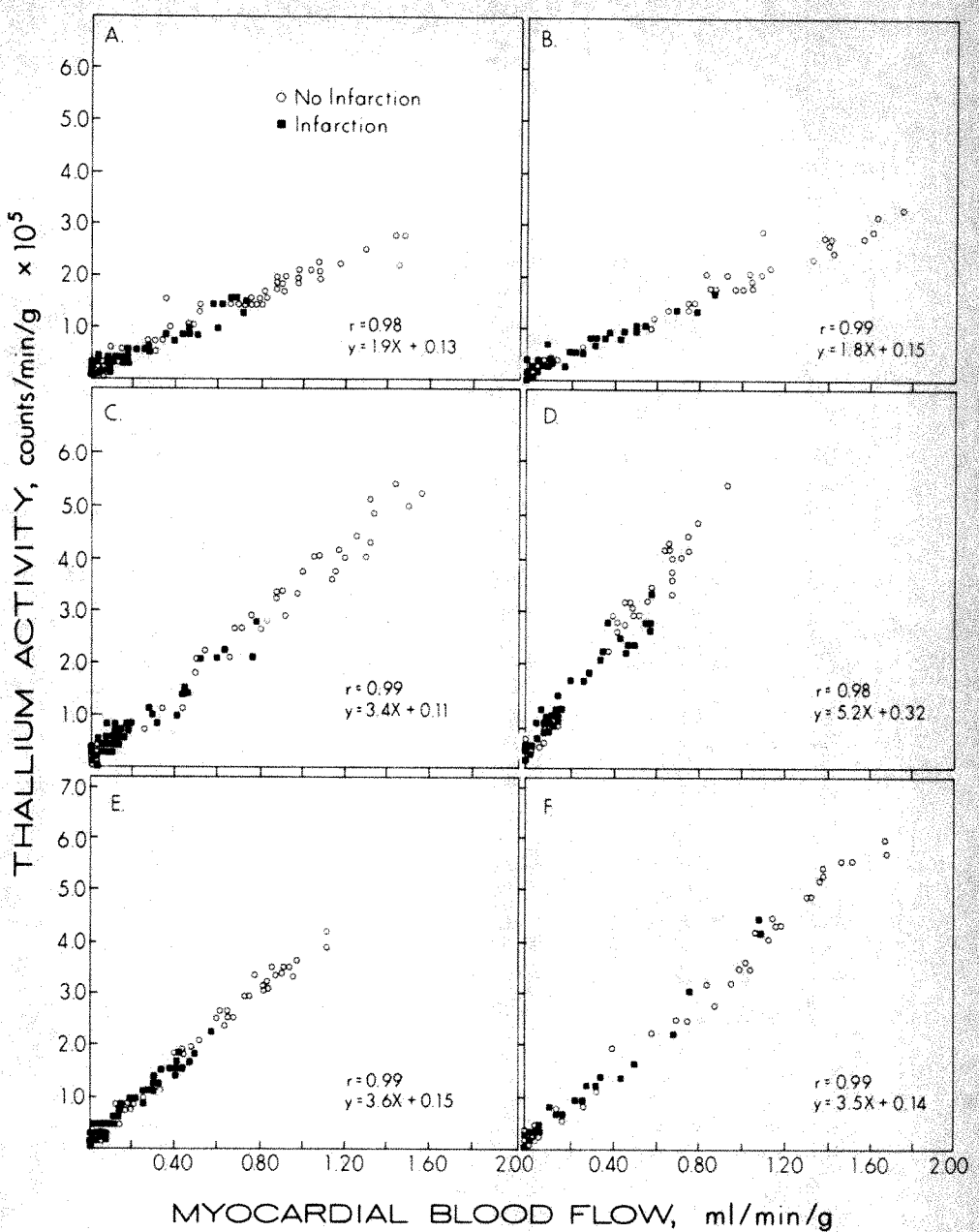

FIGURE 2. Relation between thallium-201 activity and myocardial blood flow in 6 dogs. **Closed squares** represent samples with greater than 5% histologic infarction.

Discussion

Possible limitation of thallium-201 for assessing myocardial perfusion during acute ischemia: Optimal scintigraphic assessment of myocardial perfusion in the clinical situations associated with coronary heart disease requires that myocardial localization of the imaging agent be a direct function of tissue perfusion over a wide range of reduced and increased blood flow, and variable local metabolic condition. Studies have suggested that the biologically active tracer ions such as potassium, rubidium, and thallium, which are extracted by the myocardial cell, have certain limitations as agents for accurately assessing myocardial perfusion during the variable metabolic conditions that may accompany acute or prolonged ischemia or evolving myocardial infarction, or both. Weich et al.[8] observed that the extraction fraction of thallium-201 remained constant when myocardial blood flow was altered by changing myocardial metabolic demands, but decreased when blood flow was increased in excess of metabolic demands or during systemic hypoxia or acidosis. Becker et al.[9] found a disproportionately high rubidium-86 content at very low flow rates as compared with measurements with nondiffusable inert microspheres. DiCola et al.[10] reported a close linear correlation between the distribution of thallium-201 and blood flow measured with microspheres in transmural myocardial sections 24 hours after coronary arterial occlusion. However, when the transmural samples were divided into epicardial and endocardial halves, there was a poor correlation between thallium-201 and microsphere distribution in the latter samples. The poor correlation in endocardial samples results from disproportionately

high thallium activity when blood flow was reduced less than 30% of normal.

Strauss et al.[11] reported a close linear correlation between regional blood flow determined with microspheres and thallium-201 distribution after acute coronary occlusion; thallium-201 underestimated blood flow when measurements were made during the reactive hyperemic phase after transient ischemia. In studies from our laboratory,[12] the regional distribution of thallium-201 and myocardial blood flow by microspheres was determined in dogs subjected to treadmill exercise and acute ischemia. We observed a very close linear correlation between thallium-201 localization and regional blood flow over a wide range of blood flow; in each dog blood flow was reduced to less than 0.1 ml/g per min in the ischemic region and increased 3.3 to 7.2 times resting blood flow in the nonischemic region; linear correlation coefficients were 0.98 or more in each dog.

Thallium-201 distribution in normal, ischemic, and infarcted myocardium: The purpose of the present study was to compare the initial myocardial localization of thallium-201 with simultaneous direct measurements of myocardial perfusion in normal, acutely ischemic, and recently infarcted myocardium. These conditions were chosen to simulate the potentially different pathologic conditions of reduced flow that may be encountered in the clinical use of thallium-201. Three to 4 days after initiation of infarction in the circumflex region, acute ischemia was produced in regions of the left anterior descending coronary artery. The 3 to 4 day period after acute myocardial infarction was selected to allow completion of the acute infarction process; at this interval the region subjected to prolonged ischemia was sharply delineated into infarcted and noninfarcted myocardium. The noninfarcted tissue was indistinguishable by routine histologic stains from tissue that had not been subjected to ischemia. Because substantial increases in collateral flow occur in the early days after acute coronary occlusion[13] the myocardium, which has been subjected to prolonged ischemia but which has not developed infarction, may no longer be subjected to ischemia. Thus, in samples with a mixture of normal and infarcted tissue it was not possible in the present study to determine whether blood flow to the normal tissue was normal or reduced. Although local metabolic conditions were not measured in the present study, it is possible that metabolic conditions of myocardial cells that have been subjected to no ischemia, acute ischemia, or prolonged ischemia but no infarction are different.

The results of our study demonstrate essentially identical localization of thallium-201 in these different regions when compared with direct measurements of blood flow by nondiffusable inert microspheres. These data indicate that regional myocardial perfusion is the principal determinant of initial localization of thallium-201 in each of the zones studied. Because the linear correlation coefficients approximated 1.0 and the intercepts of the regression equation were only slightly above zero in each dog, the data indicate that localization of thallium-201 very closely approximated regional perfusion over the entire range of myocardial blood flow. These data suggest that, compared with regional blood flow, the local metabolic conditions that may differ in normal and acutely ischemic myocardium and in regions containing recently infarcted myocardial tissue have inconsequential effects on initial thallium localization.

In the present study the animals were killed 5 minutes after thallium-201 and microsphere injection. Schwartz et al.[14] reported that the myocardial extraction of thallium-201 may become negative approximately 10 minutes after injection, suggesting early loss of the ion from the normal myocardium. Schwartz,[14] Pohost,[15] and their co-workers described early redistribution of thallium-201 to the ischemic region early after relief of ischemia. Thus, although the initial localization of thallium-201 may be closely related to regional perfusion over a wide range of blood flow and differing metabolic conditions, distribution at later intervals may not accurately reflect perfusion in either normal or ischemic myocardium or regions containing infarcted myocardium. These studies emphasize the need for early thallium scintigraphy after intravenous injection for optimal assessment of regional myocardial perfusion.

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Jacob Mendez DaCosta: Medical Teacher, Clinician, and Clinical Investigator

CHARLES F. WOOLEY, MD

J. M. DaCosta, a scholarly, well-trained and observant clinician, was recognized during his lifetime as a well-known authority on physical diagnosis and had an unexcelled reputation as a clinical teacher. Chairman of Medicine at the Jefferson Medical College for 19 years, president of the College of Physicians of Philadelphia in 1884 and again in 1895, he was one of the original members of the Association of American Physicians and its president in 1897. Earlier in his career, his extensive Civil War study of "a form of cardiac malady common among soldiers . . . the study of which is equally interesting to the civil practitioner" was described in his 1871 paper "On Irritable Heart; A Clinical Study of a Form of Functional Cardiac Disorder and Its Consequences." Soon labeled *DaCosta's syndrome*, the irritable heart lineage can be traced through the *soldier's heart*, the *effort syndrome*, and *neurocirculatory asthenia* in World War I, *anxiety neurosis* in World War II, and the *mitral valve prolapse syndrome* in the second half of the 20th century.

The *Jefferson Medical College Alumni Bulletin* (spring 1975) contains an article by Robert I. Wise[1] which traces the history of the Chair of Medicine at Jefferson from its origins with the founding of Jefferson Medical College on June 2, 1824, when 4 physicians were appointed by the trustees of Jefferson College of Canonsburg (now the Washington and Jefferson College) as the first faculty of the new medical college. Joseph Klapp (1 year), John Eberle (5 years), Daniel Drake (1 year), John Revere (10 years), John Kearsley Mitchell (17 years), Samuel Dickson (14 years), Jacob DaCosta (19 years), and James C. Wilson (20 years) occupied the Chair of Medicine from 1824 to 1911, the period pertinent to my quest.

The early years: Jacob M. DaCosta entered Jefferson Medical College in 1849, graduated 3 years later at the age of 19 at a time when the medical faculty included John Kearsley Mitchell (medicine), T. D. Mütter (surgery), Charles D. Meigs (obstetrics), Franklin Bache (chemistry), Robley Dunglison, Joseph Pancoast (anatomy), and Robert Huston (dean of faculty, materia medica), during a "golden age, a time of distinction and academic prosperity for Jefferson."[1]

DaCosta brought an unusual background to medical college, at a time when the educational background of many American medical students was limited or nil. He was born on the island of St. Thomas, West Indies, in a family of Spanish and Portuguese extraction. His father, John Mendez DaCosta, a gentleman of wealth and culture, descended from an English branch of the family. Jacob was 4 when his parents left St. Thomas to live in Europe, where he and his brother Charles attended a gymnasium in Dresden. Studies included the classics and modern languages, and he became fluent in French and German, with a reading knowledge of Spanish, Portuguese, Italian and Dutch. He came to Philadelphia in 1849, where his mother was then living, and entered Jefferson Medical College.

As a student of Professor Mütter, DaCosta, along with friend and fellow student John H. Brinton, conducted demonstrations of tumors and specimens removed by Mütter at his clinics. Brinton, a Philadelphian, graduated with DaCosta in 1853, later served with Grant in the Tennessee and Cumberland River Campaign in 1862, and became Professor of Surgery at Jefferson after Samuel Gross in 1882. DaCosta married Frederica Brinton in April 1860.

After graduation, DaCosta spent 18 months in Paris and Vienna, involved in the study of pathology and internal medicine. Participation in medical and cultural

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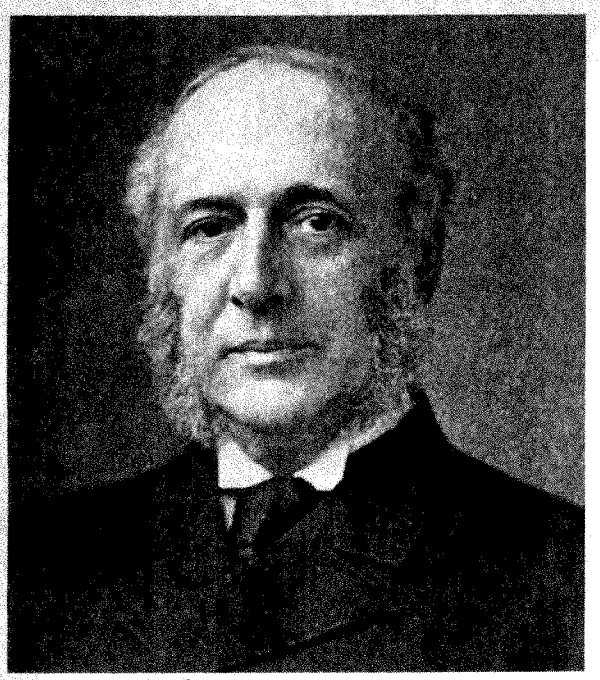

FIGURE 1. The mature DaCosta. Courtesy of the Scott Memorial Library, Thomas Jefferson University.

activities was enhanced by his knowledge of languages. He studied, attended the clinics, went to the great hospitals of Paris (Hotel Dieu, La Charité), and absorbed the wisdom of a great medical center where Robin, Claude Bernard, Verneuil, Néalton, Broca, and Trousseau were active and teaching. Trousseau, in particular, made a deep and lasting impression on the young DaCosta. Trousseau's magnificent lecture[2] on percussion began with a discussion of Auenbrueger, made the transition to Corvisart and his pupil Laennec, and traced the development of the physical examination of the chest as related to the concomitant development of urinalysis, examination by the speculum, the laryngoscope, and the opthalmoscope so "the most inaccessible organs can now be seen." Trousseau concluded with a reflection and a charge: "Rich in the possessions bequeathed to you by the physicians of the past, to you belongs the duty of uniting modern science with ancient wisdom, and of rekindling the temporarily despised torch of old medical traditions. Let this be your endeavor! It is a great and splendid aim! Fail not to pursue it!"

The impact of the Parisian teachers, and the further experiences in Prague and Vienna with August Klaatsch, Hyrtl, Skoda, Oppolzer, Bamberger, Rokitansky, and Hebra set, as Wilson[3] notes "... a clear course toward his lifework—pathological anatomy, visceral disease, the heart and lungs, and the diseases of the skin in their relation to general medicine; in a word, internal medicine in its broadest sense, the greatest of the specialties." Again, from Wilson: "He would be a teacher; at all events, he would fit himself to be one. The talent was inborn."

DaCosta returned to Philadelphia in 1853. Philadelphia, with a long tradition of leadership in American medicine, was the site of the nation's first medical school, hospital, school of pharmacy, and mental hospital. Baltzell[4] notes that in "... 1847, when the American Medical Association was founded in Philadelphia to bring order out of the chaos of standards then regulating the profession, all the officers either were practicing in the city or were graduates of the Penn Medical School; eight of the first ten presidents of the AMA trained at Penn." When DaCosta returned to this environment, he was invited to take part in the Summer Association for Medical Instruction located on Chant Street, "a place of historical interest in the medical life of Philadelphia, long famous for all kinds of extramural teaching. In this work he was associated with men somewhat older than himself, but still young, who had attracted attention as teachers and practitioners. Prominent among them were John Forsyth Meigs, Frank West, the Wallace brothers, Robert Bridges, John H. Brinton, and Addinell Hewson. To DaCosta was assigned the subject of Physical Diagnosis."[3]

DaCosta combined office practice (at 212 South Eleventh Street), instruction of students in physical diagnosis, and an appointment as a physician to the dispensary attached to the Moyamensing House of Industry.

The death of John Kearsley Mitchell in 1858 was followed by the appointment of Samuel Dickson to the Chair of Medicine at Jefferson. Dickson, trained under Physick, Dorsey, and Chapman at the University of Pennsylvania, had been one of the founders of the Medical College of South Carolina. "From this date DaCosta became closely identified with the Jefferson College, at first as an instructor of telling influence in connection with the Chair of Medicine, subsequently as clinical lecturer, and finally, in 1872, as the successor to Professor Dickson in the Chair of Practice."[3]

The Turner's Lane years: DaCosta's syndrome: The War Between the States affected Philadelphia in a unique way. Philadelphia became a major hospital center as the war progressed, and by 1865 there were 27 hospitals and 25,000 beds in or near the city. S. Weir Mitchell, son of John Kearsley Mitchell, recalled[5] that it "... became necessary to provide additional help in the hospital service, and this was supplied by employing what were known as acting assistant surgeons. They served at home, but were liable to be called into duty in the field. Except in the case of Antietam and Gettysburg this was rare. Among these were Agnew, Gross, Morton, Stillé, DaCosta, Harry Hart and many more."[5] A number of specialized infirmaries developed as the war progressed; one of these was designated by the U.S. Army Medical Department as the U.S. Army Hospital for Injuries and Diseases of the Nervous System, Turner's Lane. Weir Mitchell described the move from the building known as Moyamensing Hall on Christian Street to the Turner's Lane Hospital: "... the space proving insufficient, a surburban estate on Turner's Lane was rented in August 1862, and pavilions built for

400 men. One was assigned to DaCosta, and afforded him a chance for a classical study of exhausted hearts and for other able papers."[5]

The Turner's Lane story has been told by William Middleton[6] in a remarkable work. The contributions of S. Weir Mitchell, William Keen, and George Morehouse to clinical neurology represent an early example of the specialty approach in clinical medicine, with clinical research conducted in a controlled clinical research center. The earlier publication and recognition of these neurologic studies eclipsed the work by DaCosta from the same institution; although DaCosta presented preliminary reports of his work in 1862 and 1864, there was a long lag time from the original studies on soldiers with "irritable heart" to the publication of his definitive work in 1871.

The definitive report "On Irritable Heart: A Clinical Study of a Form of Functional Cardiac Disorder and Its Consequences"[7] is a landmark study in the history of cardiovascular disease. Jarcho[8] noted that in an era dominated by the search for organic ailments, "DaCosta's study of the condition which he named irritable heart was an attempt to cross the frontier into the obscure realm of functional disease. . . . DaCosta's paper is an impressive example of nineteenth century clinical research, conducted entirely by simple methods of history taking and physical examination without the assistance of the laboratory. The author was aided by a wise policy of the War Department, which concentrated cases of irritable heart in the hospital at Turner's Lane at Philadelphia under DaCosta's care. This favored the rapid accumulation of data and the synthesis of the clinical picture. A similar method had been in use in the hospitals of Paris and was extremely helpful if not essential to the work of Laennec and his great contemporaries."[8]

The report is a mature work by a young clinician who made good use of his knowledge of physical diagnosis, recorded and trusted his own carefully documented clinical observations, and filtered the essentials from studies of over 300 cases. After careful reflection he set forth a classic description of a clinical subject that would resurface periodically and be renamed *DaCosta's syndrome*, *soldier's heart*, *effort syndrome*, and *neurocirculatory asthenia* in World War I, *anxiety neurosis* in World War II, and the *systolic click-late systolic murmur syndrome* or the *mitral valve prolapse syndrome* in the 1960s and 1970s.[9]

DaCosta: clinical teacher: His medical treatise, "Medical Diagnosis," was published in 1864; it went through 9 editions, was intended as a guide to the knowledge and discrimination of diseases, and later appeared in German, Russian, and French translations. The approach that DaCosta used was to group morbid states "according to their marked symptoms."

DaCosta (Figure 1) was one of the founders of the successful and influential Pathological Society of Philadelphia, served as its secretary during the early years and as its president in 1864 through 1866. His early medical reports reflected his interest in pathology, and dealt with the pathologic anatomy of acute pneumonia and pancreatic cancer. He was 39 years old when he succeeded Dickson in the Chair of Practice; Wilson[3] noted that he had ". . . established himself as a successful practitioner, a teacher of the highest order, and a trusted consultant. . . . He served as physician to the Episcopal Hospital, to the Philadelphia Hospital, and to the Hospital of the Jefferson College, and was for many years consulting physician to the Childrens Hospital. . . . His clinics were models of the finest methods of medical instruction—clear, systematic, and impressive."

As a member of the staff of the Pennsylvania Hospital from 1865 until his death 35 years later, he exerted a "most important influence . . . upon the long line of resident physicians whose good fortune it was to serve with him."[3] Wilson himself was one of the physicians influenced by DaCosta, served as Chief Clinical Assistant to Professor DaCosta at Jefferson, and was appointed to Chair of Medicine when DaCosta resigned in 1891.

The historical archives at the Jefferson Library contain a "report of clinical lectures of Jacob M. DaCosta, M.D." for 1875, 354 pages of beautifully handwritten notes by Theodore Horwitz[10] submitted for the Professor DaCosta prize, which dealt with a broad spectrum of disease organized as to presentation, findings, diagnosis, and treatment. Reading through the Horwitz lecture notes and a later set by W. Wehner from 1884 to 1886, one is transported in time to DaCosta's Clinics, to eavesdrop on the professor and reflect on medical thinking of the time.

The manuscript of the valedictory address to the graduating class of the Jefferson Medical College of Philadelphia of 1891, "Professional Aspirations," contains a letter dated September 29, 1891: "My Dear Charlie, You asked me to give you the manuscript of something I have written. I give you this—my valedictory, and the last thing I wrote before resigning my Professorship. Ever affectionately, your father, J. M. DaCosta."[11]

As I reviewed the remnants of DaCosta's career, visited the archives at the College of Physicians of Philadelphia and at Thomas Jefferson University, I wondered why he is little known and honored within and without Philadelphia. After all, DaCosta, ". . . in the opinion of F. H. Garrison was probably the most able teacher of his time in the Eastern states,"[8] and Stone observed that he was ". . . perhaps the best know authority on physical diagnosis in this country, and for the past thirty years has had an unexcelled reputation as a clinical teacher."[12] He did not move once he was established at Jefferson, nor did he write a great deal, and these may be the important factors. The significance and originality of his Civil War researches have yet to be fully appreciated. He did not have the benefit of strong public relations (such as exists at Harvard, Hopkins, or the Rockefeller) during his lifetime or during this century. The class structure and cultural atmosphere of Philadelphia, as articulated by Baltzell,[4]

wherein the Quaker traits of modest behavior and gentlemanly decorum interfere with the assumption of dominant leadership roles, deserve serious consideration. The replacement of the master clinician-teacher in the medical heirarchy by the scientific researcher, coupled with gradual erosion of Philadelphia's early medical leadership role, must rank as contributing factors.

Mary A. Clarke,[13] for many years DaCosta's private secretary, wrote a richly detailed memoir which appeared in the *American Journal of Medical Science* in 1903, and supports Baltzell's Philadelphia Gentleman's hypothesis: "Dr. DaCosta was greatly opposed to the publications of biographical sketches of the living, and invariably refused to give information concerning himself for such projected works. Only after Harvard had conferred upon him, in 1897, the degree of L.L.D., and at the urgent request of the editors of the *Harvard Graduates' Magazine*, he furnished them a brief sketch of his life, which has been made use of by other journals."

Although reticent about publication of details of his personal life, Wilson[3] tells us that DaCosta had "a deep interest in the welfare of the organized profession, an interest he maintained throughout his life." His leadership qualities were manifest as chairman of a major department at a major medical college for 19 years, in the College of Physicians of Philadelphia as a Fellow (1858) and its president in the line of Redman and Shippen in 1884 and 1855 and again a decade later from 1895 to 1898, and as one of the original members of the Association of American Physicians and its President in 1897.

It seems fitting to recall Jacob Mendez DaCosta for many reasons—as an early American clinical investigator working in a clinical research center (Turner's Lane), as a patron for unsung clinicians and teachers in medical schools, as an example of the finest qualities of the Philadelphia medical spirit, and as a noble man and physician. At a time when ambition and commercialism have confused the current medical leadership, hierarchy, and membership as to the essential roles and function of physicians, the simplicity, the directness of purpose, and the essential nobility of the man deserve recall and incorporation into our individual lives. It certainly seems reasonable to search for his qualities within ourselves and among all students of medicine.

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Hypothesis: Is Congestive Cardiomyopathy Caused By a Hyperreactive Myocardial Microcirculation (Microvascular Spasm)?

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In most congested, dilated cardiomyopathies, pathologic analysis reveals focal myocardial necrosis, microscopic scarring, interstitial fibrosis, and myocellular hypertrophy. The focal nature of these processes indicates that the cardiomyopathies may not be due to diffuse abnormalities of cardiac muscle cells, at least in the early stages, but that the changes may represent focal events affecting discrete, small volumes of tissue. Experimental evidence of microvascular hyperreactivity (spasm), both in the hereditary cardiomyopathy of the Syrian hamster and in the acquired cardiomyopathy of the hypertensive-diabetic rat, suggests that transient spasm of the myocardial microcirculation may lead to focal myocellular necrosis and scarring, which then causes the unaffected myocardial cells to undergo compensatory hypertrophy in order to normalize the increased load per unit of myocardium. When enough myocardium is lost and the compensatory hypertrophy results in decreased contractility, congestive heart failure ensues as a systemic response to altered ventricular function. The efficacy of verapamil therapy in the Syrian hamster in preventing microvascular spasm, cell necrosis, and the subsequent development of a cardiomyopathy has provided hope that similar preventive treatment can be applied to patients with early stages of cardiomyopathy.

Diminished or inadequate myocardial contractility is a common manifestation of congestive cardiomyopathy, which may lead to clinically apparent congestive heart failure with all of its attendant effects on the peripheral and pulmonary circulations. It is generally believed that ventricular dysfunction in most cardiomyopathies results from diffuse involvement of cardiac muscle cells, whether due to an idiopathic insult or due to damage induced by viral agents, disturbed metabolism, or toxins (such as alcohol).[1–3] Although hereditary metabolic diseases such as alpha-1,4 glucosidase deficiency (Pompe's type II glycogen storage disease) may, in fact, result in *diffuse* myocellular changes,[4] most congestive cardiomyopathies do not demonstrate homogeneous myocardial changes when evaluated histologically. Even experimental or clinical genetic diseases primarily affecting skeletal and cardiac muscle (such as Syrian hamster cardiomyopathy and Duchenne's muscular dystrophy) typically manifest *focal* myocardial lesions.[5–7] Thus the explanation for abnormal myocardial contractility often is not evident from morphologic analysis of cardiac tissue in these diseases.

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Pathologic Features of Congestive Cardiomyopathy

The pathologic features[1–3,8–11] of most congested, dilated cardiomyopathies, whether primary or secondary, are nonspecific and cannot be employed to make a diagnosis of "heart muscle disease" without corresponding clinical or laboratory findings. Grossly, one sees a large, flabby, or firm heart with prominent ventricular dilatation. Microscopically, there may be all or a combination of the following changes: (1) interstitial fibrosis or edema surrounding individual or groups of seemingly viable myocardial cells; (2) loose or compact connective tissue encircling the microvasculature and the larger muscular vessels; (3) very discrete, sharply delimited zones of acute myocytolytic necrosis which

organizes into microscopic or confluent macroscopic scars; (4) intimal and medial sclerosis and hypertrophy of intramyocardial muscular vessels, often causing luminal compromise; and (5) varying degrees of myocellular hypertrophy. None of these features is characteristic solely of cardiomyopathy; they are frequently present in the hearts of patients with significant obstructive coronary artery disease.

Hypothesis

Because the changes just described are focal and nonspecific, most investigators have assumed that uninvolved myocardial cells are abnormal biochemically or functionally. Surprisingly little evidence has been accumulated to support this view. Abnormalities have been identified, but they are often insignificant, or more related to severe congestive heart failure than to the condition that led to that failure.[12] When care has been taken to select myocardium from uninvolved regions of cardiomyopathic hearts, analysis of ultrastructure generally reveals changes consistent with cellular hypertrophy, and biochemical or histochemical features are only slightly deviated from normal, if at all.[3,5,8,13–15] Nonselective techniques (blind biopsy sampling or tissue homogenization) often demonstrate significant changes such as increased lysosomal enzyme activity, changes in contractile proteins, and deranged mitochondrial and sarcoplasmic reticulum function.[5,16–18] Although such data are employed to support the concept of diffuse, homogeneous myocellular disease, in fact, they can also be considered to represent an admixture of heterogeneous normal and abnormal tissue.

We present herein an alternative hypothesis concerning the pathogenesis of at least some congestive cardiomyopathies, while recognizing that the mechanisms described may be generalized phenomena. We believe that the development of cardiomyopathy is related to progressive and additive *focal cellular necrosis*, and associated replacement myocardial fibrosis, and that these processes may in some cases be mediated by *dynamic alterations in the myocardial microcirculation*.[19–24] An abnormal microcirculation also could lead to the deposition of interstitial connective tissue around viable myocytes and blood vessels, which may limit diastolic compliance ("stiff heart") or interfere with cellular nutrition. Compensatory hypertrophy may be superimposed on these processes, but eventually progressive hypertrophy may be associated with decreased contractility.[25,26] When a threshold number of nonregenerating myocardial cells undergo necrosis or are affected by connective tissue deposition over time, a sufficient derangement of ventricular function may ensue which is clinically manifested as the syndrome of congestive heart failure. This is analogous to the abrupt loss of large volumes of tissue due to a myocardial infarction producing chronic failure or acute cardiogenic shock. However, the slow, relentless, and even subclinical nature of the cardiomyopathic process has obscured the similarities between the 2 conditions.

Models of Cardiomyopathy

We have identified dynamic microvascular alterations in several experimental cardiomyopathies.

The Syrian hamster,[5,7,24] a heritable model of muscular dystrophy and congestive cardiomyopathy, develops focal myocytolytic necrosis of the heart at approximately 30 days of age, which continues actively for 3 to 4 months with hypertrophy of uninvolved cells and results in congestive heart failure within the first year of life. Pathologic analysis of these hearts reveals discrete zones of focal ventricular necrosis and fibrocalcific scarring, with insignificant alterations in the unaffected myocytes. The pattern of necrosis, with *groups* of cells undergoing myocytolysis sharply delimited from surrounding normal myocardium, is consistent with mediation by the microvasculature. Myocytolysis is a form of muscle necrosis commonly associated with increased levels of or hypersensitivity to endogenous or exogenously administered catecholamines[27]; however, it may also be produced by transient occlusion of a coronary vessel followed by reperfusion.[28] Despite a possible relation to the coronary microvasculature, histologic and ultrastructural studies have revealed no fixed anatomic obstructive lesions in the microcirculation of these animals.

In an attempt to define a dynamic microcirculatory lesion, we perfused hamster hearts while they were beating with a silicone rubber solution (Microfil®) which completely fills the microcirculation and hardens in situ. By clearing the tissues, we observed a 3-dimensional array of small vessels down to the capillary level, analogous to a microangiogram, with the vessels visualized as in a stop-frame at the moment of death. In the cardiomyopathic animals, we frequently identified arterioles and capillaries with areas of focal narrowing consistent with spasm (Fig. 1), with no anatomic obstruction in these vessels.[20,24] Since the presence of a stenotic zone within a vessel lumen of normal caliber can be explained only by structural deformation of the vessel or contraction of its wall (spasm), we believe that the absence of disease in the vessel wall is evidence that the process is secondary to spasm. These focal, narrowed zones were extremely rare in the control hearts. The calcium blocking agent verapamil, which can prevent the development of necrosis in hamster hearts, also prevented the microvascular spasm, presumably because it is a potent smooth muscle relaxant and coronary vasodilator.[21,24] Thus, focal necrosis in these hearts, which is the major pathologic feature of the disease, may result from transient and focal spasm of the microcirculation supplying small groups of myocardial cells.

Although these observations suggest a possible pathogenetic mechanism in hamster cardiomyopathy, they must be viewed with caution. We do not claim that the microvascular spastic lesions identified with our methods are causally related to specific myocardial necrotic foci. Rather, it is likely that they indicate a general hyperreactivity of the microcirculation, possibly stimulated by the introduction of anesthesia, surgical manipulations, or Microfil perfusion. However, the

vascular changes do appear to be markers of a difference between cardiomyopathic and normal animals, because they were virtually absent in the controls. Furthermore, the lesions were prevented with verapamil therapy, implying that they were not artifactually induced. The effectiveness of verapamil in this regard suggests that it may act primarily on the microcirculation; however, we cannot rule out the possibility that the drug acts directly on the myocardial cells to prevent necrosis. Studies with vasodilators which do not interact with myocardial cells are necessary before definitive conclusions can be drawn about this disease.

A question crucial to the hypothesis is whether transient obstruction of the microcirculation can produce small areas of myocardial necrosis. This would require that the microcirculation be arranged as an end-vessel system; otherwise, intercapillary anastomoses could supply transiently ischemic cells with sufficient substrate to maintain viability. In fact, we have shown that the microcirculation is arranged into capillary loops without intercapillary connections in the dog[29] and recently in humans,[30] and we have reason to believe that a similar pattern exists in rodents (personal observations, 1981). We also have shown that embolization of 25 to 50 μm microspheres into the microcirculation of dogs or rats produces focal necrosis very similar to that seen in the hamster.[31] Variation in the size of the necrotic lesion may depend on the size of the vessel occluded, and could account for similar variability in clinical or experimental diseases. It is interesting that these microembolic phenomena appear secondary to vasospasm, as necrosis can be prevented with alpha-adrenergic blockade.

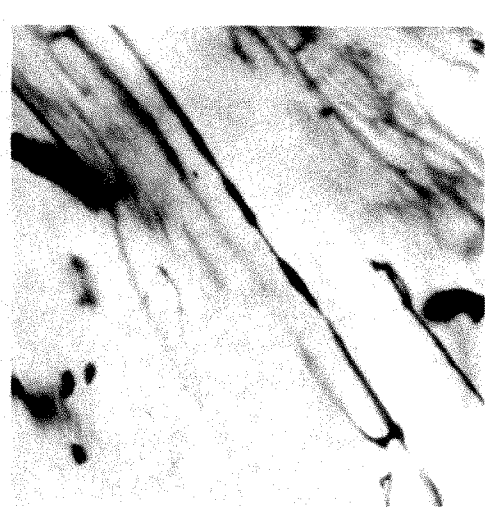

FIGURE 1. Silicone rubber (Microfil) perfused microcirculation in a 50 day old cardiomyopathic hamster, studied during the period of active myocardial necrosis. The precapillary vessel in the center of the field has several discrete areas of narrowing, with pre- and poststenotic dilatation of the lumen. Other studies of similar vessels have demonstrated no anatomic lesions associated with these narrowed zones, thus supporting the view that these stenoses are secondary to hyperreactivity or spasm of the vessel wall. (Transilluminated, cleared myocardium; magnified X150, reduced 19 percent.)

For the mechanisms suggested by our observations in the hamster to have applicability to other forms of heart muscle disease, additional models must be evaluated. In this regard, we have identified very similar features of myocytolytic necrosis, fibrosis, and cellular hypertrophy in an acquired cardiomyopathy initially described clinically and subsequently produced in animals.[10,11] Hypertensive-diabetic cardiomyopathy in both humans and rats is characterized by numerous foci of myocytolytic necrosis. In contrast to Syrian hamster cardiomyopathy, however, extensive interstitial connective tissue (collagen and basement membrane material) is also deposited around vessels and hypertrophied myocardial cells. In studies of the microcirculation in the rat model employing silicone rubber perfusions in vivo, a multiplicity of microvascular constrictions, tortuosities, and microaneurysms were identified.[19,22,23] These lesions, which appear consistent with microvascular spasm, may account for the extensive myocytolytic necrosis in these hearts. Interstitial fibrosis, however, may result from increased "leakiness" of the microcirculation secondary to the combined effects of hypertension elevating perfusion pressure and diabetes mellitus damaging the vessel wall. We do not know yet whether the morphologic changes in this disease can be prevented with vasodilator therapy, although this will be a crucial test of the hypothesis.

Conclusion

Lesions consistent with microvascular hyperreactivity (spasm) observed in several models of cardiomyopathy suggest that dynamic vessel obstruction may lead to the focal cell necrosis and subsequent fibrosis characteristic of these diseases. The similarity of these paradigms of human disease to other cardiomyopathies suggests that comparable microcirculatory events may be a feature of congestive cardiomyopathy in general. To test the hypothesis, additional studies of other cardiomyopathic models will be required to determine whether lesions can be identified in the microvasculature. The ultimate test will be whether such lesions can be prevented with the use of vasodilators which do not affect the myocardial cell, thereby preventing the development of cardiomyopathy. In addition, longitudinal studies in which multiple foci of micronecrosis are produced with microemboli or catecholamines will be important to determine whether summated myocardial insults can lead to cardiomyopathy. If the results of such studies are consistent with our preliminary observations, then the hypothesis presented herein may provide an insight into the pathogenesis of congestive cardiomyopathy and will serve to shift the focus in this condition away from the myocardium to the microcirculation. Rational therapy may thereby be advanced for this disorder in man.

Acknowledgment

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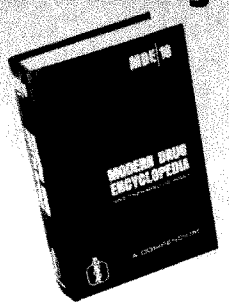

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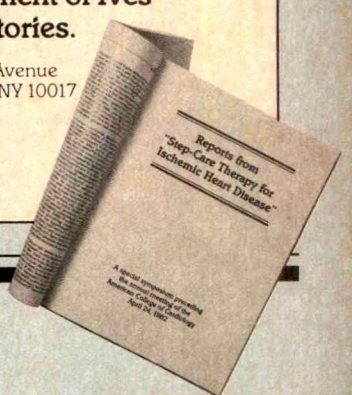

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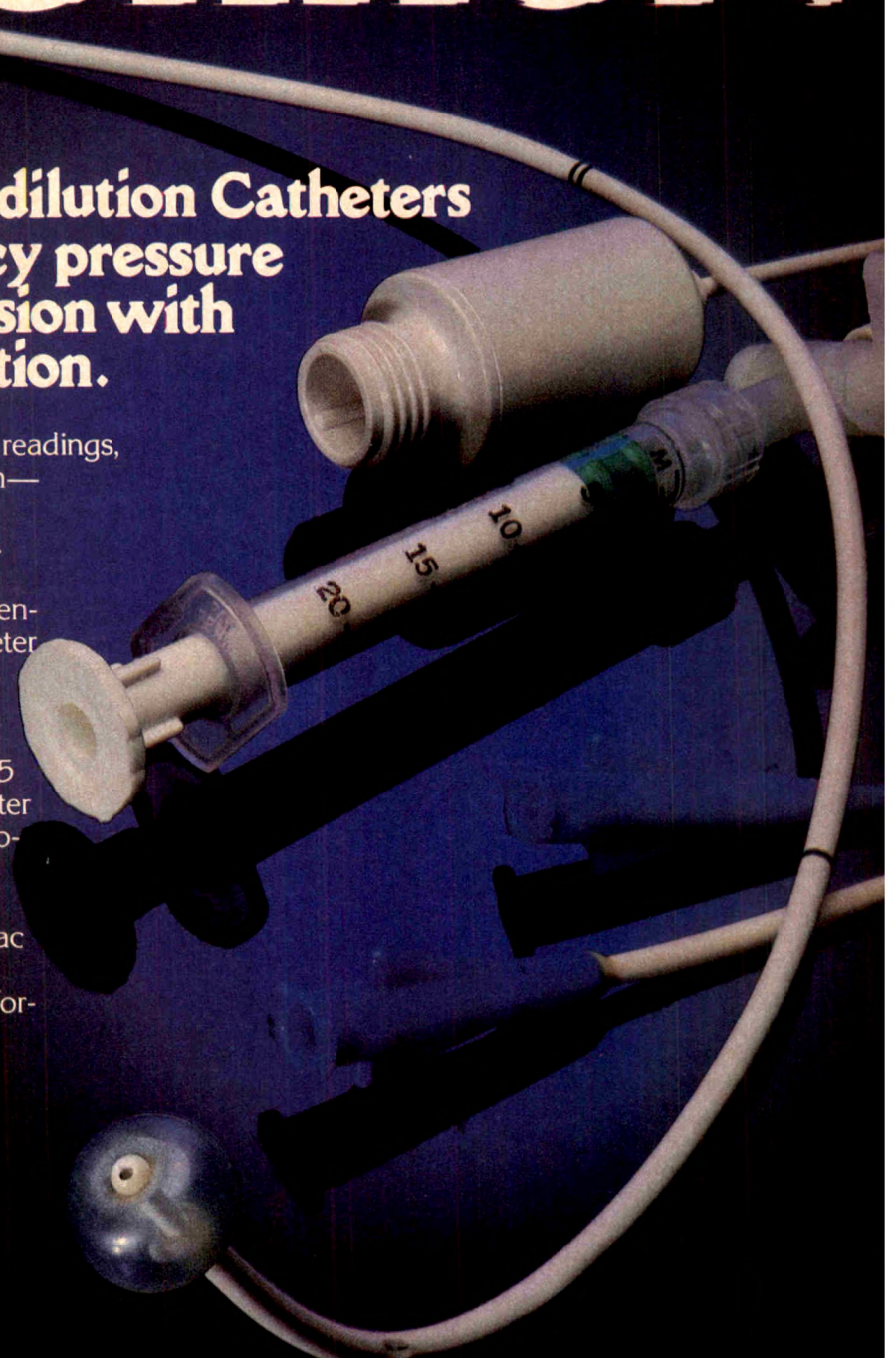

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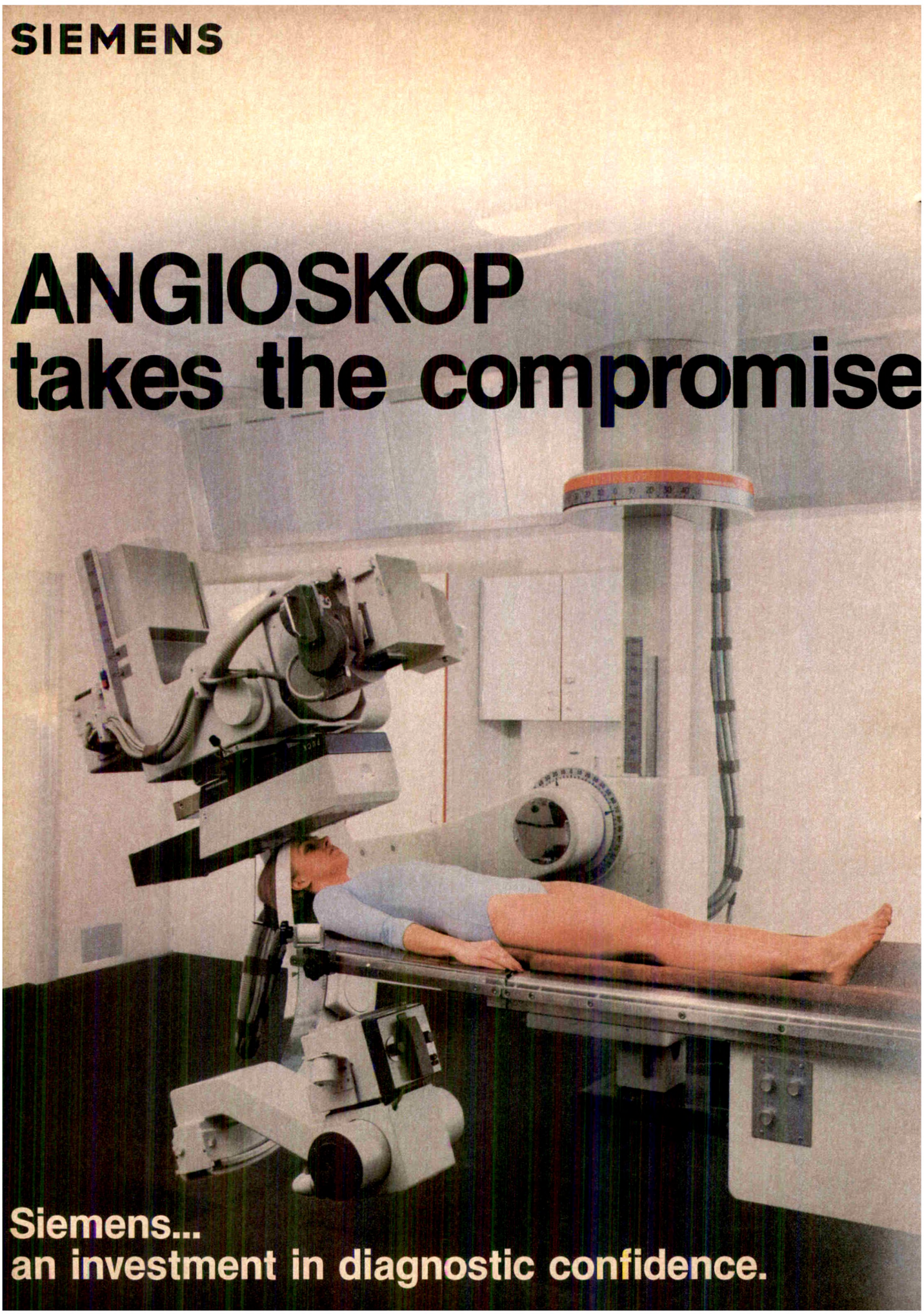

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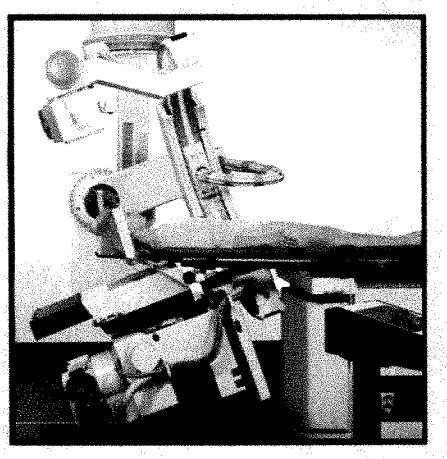

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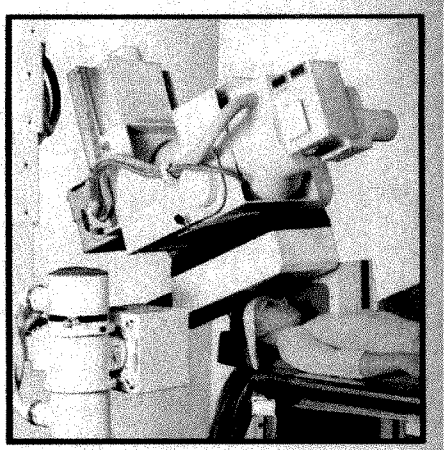

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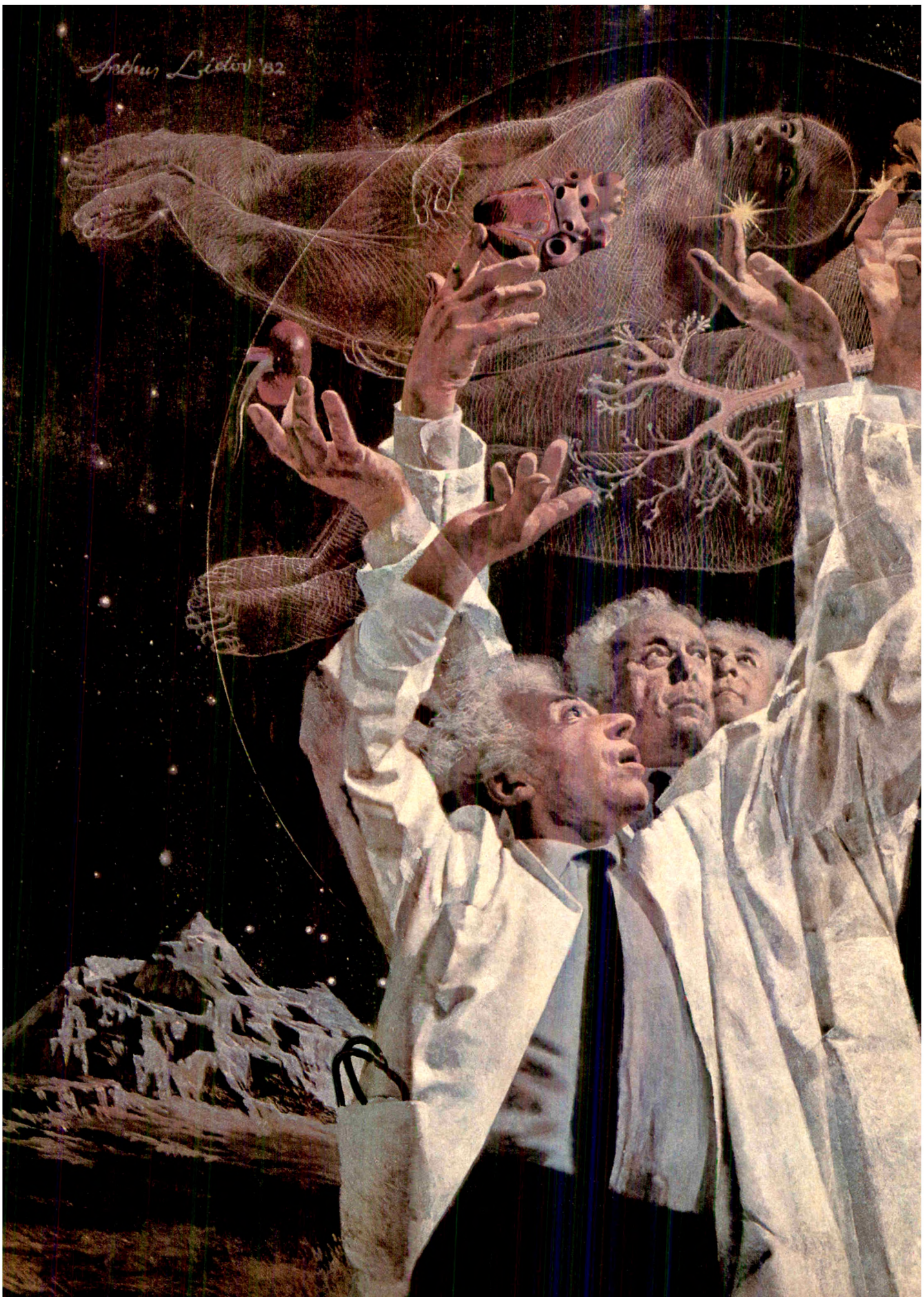
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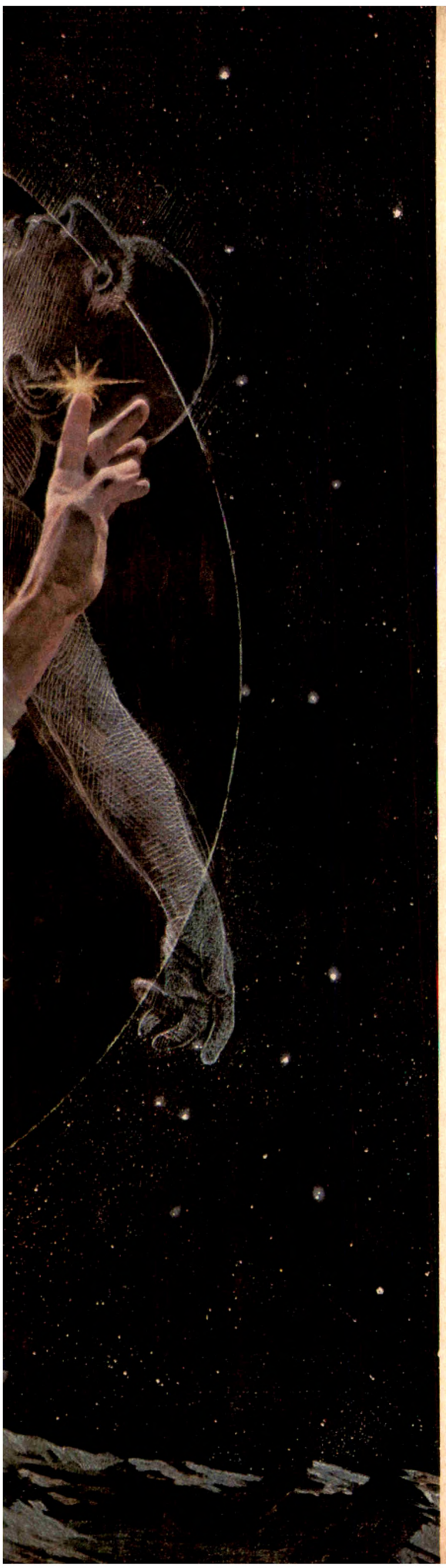

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*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

**Like any antihypertensive, use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

1. Statement on Hypertension in the Elderly, Revised April, 1980. Approved by the National High Blood Pressure Education Program Coordinating Committee.

Tablets of 0.1, 0.2, 0.3 mg

Catapres®

(clonidine HCl)

Hypertension

Please see brief summary of PI for warnings, precautions, and adverse reactions.

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Tablets of 0.1, 0.2, 0.3 mg

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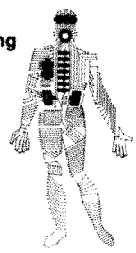

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Tablets of 0.1, 0.2, 0.3 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000 and unit dose package of 100. Also available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

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Total no. copies printed (Net Press Run)	29,736	29,000
Paid circulation		
1. Sales through dealers and carriers, street vendors and counter sales	-none-	-none-
2. Mail subscriptions	26,968	26,721
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Free distribution by mail, carrier or other means, samples, complimentary, and other free copies	696	657
Total distribution (Sum of C and D)	27,664	27,378
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Norpace
(disopyramide phosphate) 100-mg and 150-mg capsules

Norpace CR controlled release
(disopyramide phosphate) 100-mg and 150-mg capsules

Before prescribing Norpace (disopyramide phosphate) or Norpace CR, please consult current complete prescribing information, a summary of which follows: **Indications**: For suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion). Norpace is equally effective in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Norpace CR should not be used initially if rapid establishment of disopyramide plasma levels is desired. Oral disopyramide phosphate has not been adequately studied in patients with acute myocardial infarction or with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established. **Contraindications**: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug. **Warnings: Norpace or Norpace CR may cause or worsen congestive heart failure (CHF) or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily with primary cardiomyopathy or inadequately compensated CHF. Norpace or Norpace CR should not be used in patients with uncompensated or marginally compensated CHF or hypotension unless the condition is secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace or Norpace CR, but careful attention must be given to maintaining cardiac function, including optimal digitalization. If hypotension occurs or CHF worsens, Norpace or Norpace CR should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace or Norpace CR should be discontinued if significant widening (greater than 25%) of the QRS complex occurs. Prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. If Q-T prolongation greater than 25% is observed and if ectopy continues, the patient should be monitored closely, and discontinuation of Norpace or Norpace CR considered. In rare instances significant hypoglycemia has been reported during Norpace or Norpace CR therapy. The concomitant use of Norpace or Norpace CR with other Type 1 antiarrhythmic agents should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. Patients receiving more than one antiarrhythmic drug must be carefully monitored. If first-degree heart block develops, the dosage of Norpace or Norpace CR should be reduced. If the block persists, continuation of Norpace or Norpace CR must depend upon an assessment of benefit versus risk. Development of second- or third-degree AV block or uni-, bi-, or trifascicular block requires discontinuation of Norpace or Norpace CR, unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic activity, disopyramide phosphate should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken. Precautions**: Patients with atrial flutter or fibrillation should be digitalized prior to Norpace or Norpace CR administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace or Norpace CR is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of disopyramide phosphate. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage. Norpace CR is not recommended for patients with severe renal insufficiency. Antiarrhythmic drugs may be ineffective in patients with hypokalemia, and their toxic effects may be enhanced in patients with hyperkalemia. Therefore, potassium abnormalities should be corrected before starting Norpace or Norpace CR therapy. Safe use in pregnancy has not been established. Disopyramide has been found in human fetal blood. **Norpace has been reported to stimulate contractions of the pregnant uterus.** Use of Norpace or Norpace CR in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. Following oral administration, disopyramide has been found in human milk at a concentration not exceeding that in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted. Effects of Norpace or Norpace CR on the fetus during delivery or on the course of labor and delivery are unknown. **Adverse Reactions**: Dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention, urinary frequency and urgency, impotence, nausea, pain/bloating/gas, anorexia, diarrhea, vomiting, nervousness, dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains, hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain, generalized rash/dermatoses, itching, hypokalemia, elevated cholesterol/triglycerides, depression, insomnia, dysuria, numbness/tingling, elevated liver enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, and hypoglycemia. Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported, as have fever, respiratory difficulty, thrombocytopenia, and gynecomastia. **Dosage and Administration**: Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses. The recommended dosage schedule for most adults is either 150 mg every six hours for immediate-release Norpace or 300 mg every 12 hours for Norpace CR. For patients less than 110 pounds (50 kg) the recommended dosage is either 100 mg every six hours for immediate-release Norpace or 200 mg every 12 hours for Norpace CR. If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg of immediate-release Norpace every six hours, with subsequent dosage adjustments made gradually with close monitoring. **See current complete prescribing information for dosage recommendations, including pediatric use.**

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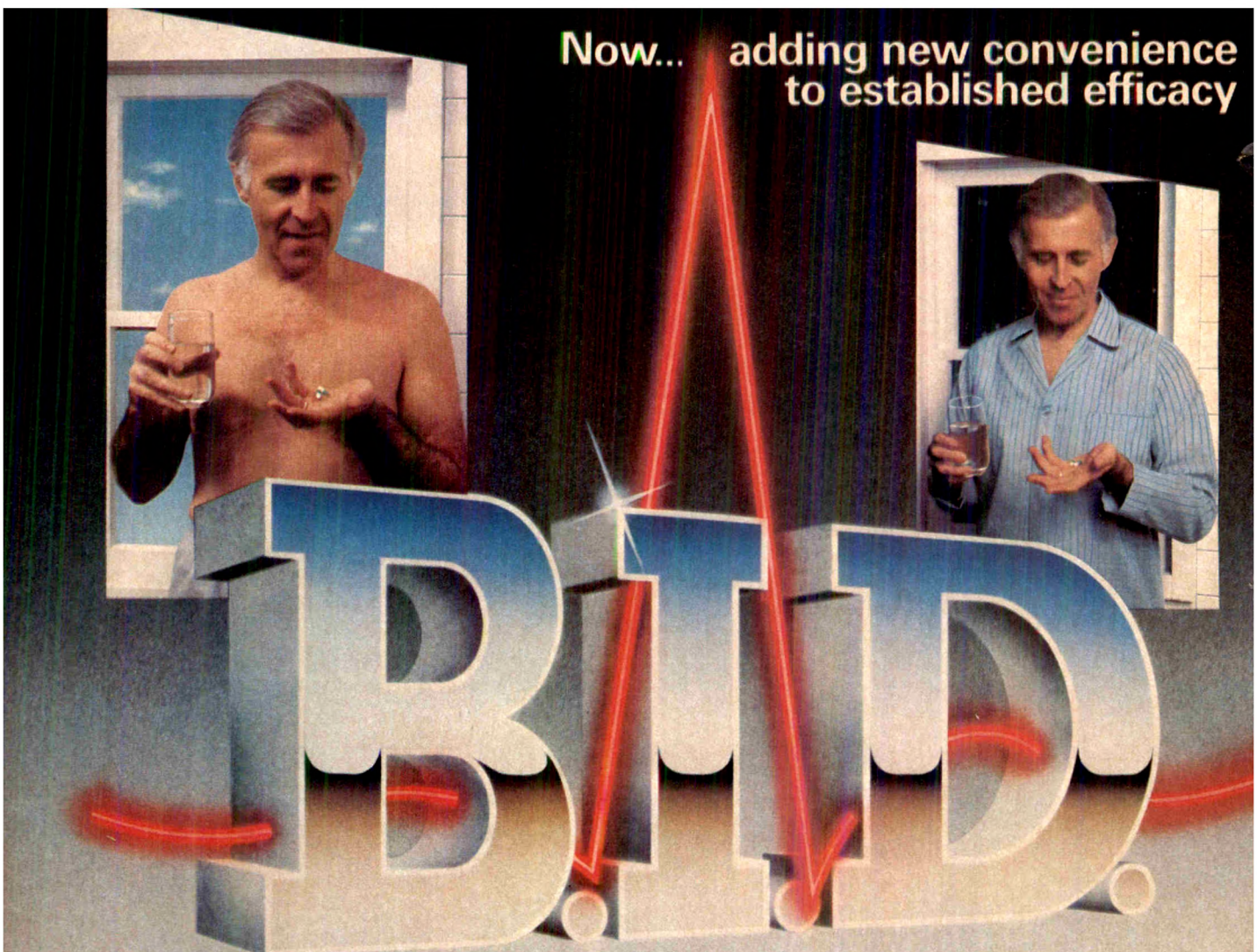

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(disopyramide phosphate)

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Effective dysrhythmia therapy *Bioavailability studies demonstrate that Norpace CR q12h provides therapeutic blood levels equivalent to immediate-release Norpace (disopyramide phosphate) q6h, with less variability.*

The most commonly seen side effects from disopyramide phosphate are anticholinergic, and the most severe are due to its negative inotropic properties. Please see the brief summary of prescribing information on the preceding page.

SEARLE

SYMPOSIUM ON VERAPAMIL THERAPY FOR ANGINA PECTORIS
PART III: STUDIES IN EFFORT-RELATED ANGINA

MILTON PACKER, MD, Guest Editor, and WILLIAM H. FRISHMAN, MD, Guest Co-Editor

Verapamil Therapy for Stable Exertional Angina Pectoris

DONALD A. WEINER, MD, and MICHAEL D. KLEIN, MD

Clinical and exercise responses to therapy with the calcium-channel blocking agent verapamil were assessed in 26 patients with stable exertional angina pectoris using a double-blind, placebo-controlled, randomized crossover study design. Verapamil, 480 mg daily, reduced the frequency of angina attacks (5.6 ± 7.3 to 2.2 ± 3.0 attacks per week, $p < 0.001$) and number of nitroglycerin tablets consumed (3.4 ± 4.9 to 1.2 ± 2.5 tablets per week, $p < 0.05$), and increased exercise duration (6.4 ± 2.1 to 7.5 to 1.8 minutes, $p < 0.001$) (all data are mean ± standard deviation). These changes were significantly better than those seen with placebo. These beneficial effects of verapamil were related to significant reduction in the heart rate-systolic blood pressure product during submaximal exercise. Adverse effects from verapamil were few and consisted primarily of constipation in 6 patients. A total of 193 patients had been entered in 6 independent clinical trials, which have compared verapamil with placebo for the treatment of stable exertional angina pectoris, using a similar study design. The combined evidence from all these studies indicates that verapamil is a highly effective and safe drug for the treatment of stable effort-related angina pectoris.

Conventional drug therapy for the treatment of exertional angina pectoris has relied on the use of nitrate preparations[1,2] and beta-adrenergic blocking agents.[3,4] These medications reduce the major determinants of myocardial oxygen demand at rest and during any level of exercise.[5,6] In some patients, however, troublesome side effects can occur.[7] Other patients fail to achieve satisfactory remission of symptoms, even with combinations of these drugs.

A new class of antianginal drugs which inhibit the influx of calcium ions across myocardial and vascular smooth muscle and reduce automaticity in sinoatrial cardiac pacemaker cells[8] has been developed. These pharmacologic actions serve to reduce heart rate and systolic blood pressure, which might benefit patients with exercise-induced angina pectoris.[9-11]

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This study reports the subjective and objective improvement in 26 patients with stable angina of effort treated with the calcium entry blocker drug verapamil. The results of this trial, published previously,[12] are reviewed together with the results of 6 other studies, all of which utilized a double-blind, placebo-controlled, crossover study design.

Methods

Patient population: Twenty-six men with a mean age of 55 years (range 30 to 72) were enrolled in the protocol during a 17 month period. The selection criteria included a minimum of 5 episodes of angina pectoris per week in a stable pattern and an abnormal control treadmill test with both ischemic (1 mm or greater) S-T segment depression and angina during exercise testing. All patients had either a radionuclide or angiographic left ventricular ejection fraction greater than 40%.

Study design: The precise details of the protocol have been reported elsewhere.[12] In brief, it consisted of the following phases: an initial 2 week, placebo stabilization phase; a single-blind phase in which 2 doses of verapamil, 320 and 480 mg per day in 4 divided doses, were tested sequentially for 1 week

periods; and a double-blind, randomized phase in which the patients received either placebo or verapamil, 480 mg per day, for 2 week periods, followed by a 1 week drug tapering period. A 1 week buffer period separated the two randomized phases.

Data collection: Subjective evaluation consisted of analyzing a diary in which the patients recorded the number of anginal attacks and nitroglycerin tablets consumed. Objective evaluation included data recorded during performance of 8 treadmill exercise tests using the Bruce protocol[13] during the 12 week protocol. The heart rates and blood pressures were recorded at rest, during submaximal exercise (defined as the end of stage 1 of exercise), and at maximal exercise. The peak S-T segment depression, the time from the start of exercise to the onset of 1 mm of S-T segment depression, and the total duration of exercise were also analyzed.

Statistics: One-way analysis of variance was used to determine whether there was significant difference in the group mean values. If the analysis of variance indicated a significant difference in the mean values for a parameter, a two-tailed Student's t test was applied. Probabilities were considered significant at the 0.05 level. All values are expressed as means ± standard deviation.

Results

Single-blind phase: In the single-blind phase, the 26 patients reported subjective improvement during therapy with verapamil. The mean frequency of anginal attacks decreased from 11.7 ± 8.7 attacks per week on placebo to 3.7 ± 6.0 attacks per week on verapamil, 320 mg daily, and to 3.7 ± 5.8 attacks per week on verapamil, 480 mg daily (placebo versus both dose levels of verapamil, $p < 0.05$) (Fig. 1). Nitroglycerin consumption was also significantly reduced during therapy with both doses of verapamil compared with placebo: from 4.5 ± 5.7 tablets per week with placebo to 1.9 ± 3.1 tablets per week with verapamil, 320 mg, and 2.1 ± 4.0 tablets per week with verapamil, 480 mg ($p < 0.05$). The differences observed between the lower and higher doses of verapamil were not significant. Objective improvement was also documented by a significant ($p < 0.001$) increase in exercise duration during therapy with verapamil, 320 mg per day (6.9 ± 2.3 minutes) and 480 mg per day (8.0 ± 1.7 minutes) as compared with placebo (5.1 ± 1.6 minutes). The exercise duration with the higher dose of verapamil was significantly greater than that seen with the lower dose (Fig. 2). The peak S-T segment depression during exercise was significantly reduced with verapamil compared with placebo only at the higher dose of verapamil (Fig. 3).

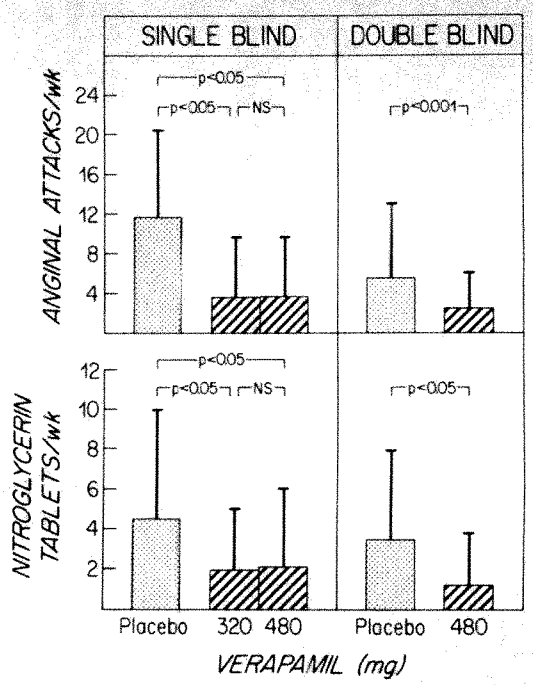

FIGURE 1. Effect of verapamil therapy compared with placebo in the number of anginal attacks and nitroglycerin tablets ingested per week in the single-blind and double-blind phases. Values are expressed as mean ± standard deviation.

Double-blind phase: Since, during the single-blind phase, no patient had major adverse effects with the higher dose of verapamil and many showed increased exercise tolerance with higher compared with lower doses of the drug, every patient was treated with either 480 mg of verapamil or identical placebo capsules during

TABLE I Previous Double-Blind Placebo-Controlled Studies Evaluating the Efficacy of Verapamil

	Neumann et al.[14]	Phear[15]	Andreasen et al.[16]	Bala Subramanian et al.[11]	Pine et al.[17]	Tan et al.[18]
Patients (n)	30	20	47	28	30	12
Males (n)	15	13	38	25	30	12
Mean age or age range (yr)	80	58	60	43–69	57	58
Daily dose of verapamil (mg)	120	240	240	360	240, 360, 480	320
Evaluation period (wk)	6	2	4	2	4	4
Effects of verapamil						
Anginal attacks per week	Not reported	No improvement	Decreased 25%	Decreased 72%	Decreased 46%	Decreased 78%
Nitroglycerin tablets per week	Decreased 27%	Not reported	Decreased 25%	Decreased 78%	Decreased 55%	Not reported
Exercise time	Not reported	Not performed	Increased 20% (n = 17)	Increased 70%	Increased 70% (n = 18)	Increased 20%

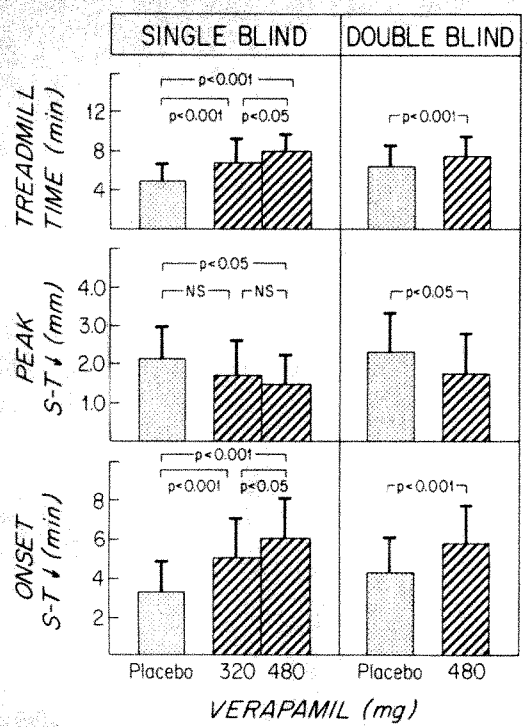

FIGURE 2. Effect of verapamil therapy compared with placebo on treadmill time, peak S-T segment depression, and time to onset of S-T segment depression in the single-blind and double-blind phases. Values are expressed as mean ± standard deviation.

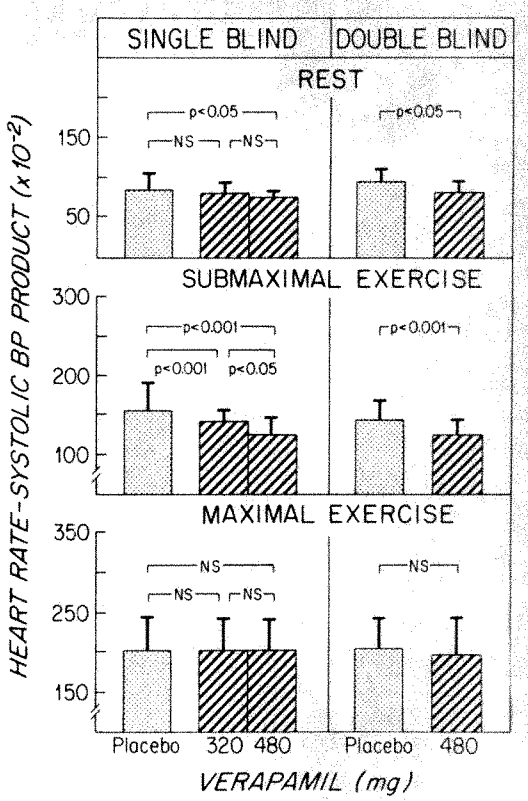

FIGURE 3. Effect of verapamil therapy compared with placebo on the product of the heart rate and systolic blood pressure at rest, and submaximal and maximal exercise in the single-blind and double-blind phases. Values are expressed as mean ± standard deviation.

the randomized double-blind crossover phase. During the double-blind phase, patients obtained benefits from verapamil that were similar to those seen during the single-blind trial. Verapamil reduced mean anginal frequency (from 5.6 ± 7.3 to 2.2 ± 3.0 attacks per week, $p < 0.001$) nitroglycerin consumption (from 3.4 ± 4.9 to 1.2 ± 3.0 tablets per week, $p < 0.05$, Fig. 1), and the rate-pressure product at rest and during submaximal exercise (Fig. 2). Verapamil increased the time to onset of 1 mm S-T segment depression (Fig. 2) and increased exercise duration (from 6.4 ± 2.1 to 7.5 ± 1.8 minutes, $p < 0.001$, Fig. 3). Not all patients responded to verapamil therapy with a marked increase in exercise duration, however. Ten patients had only a modest (less than 10%) increase in exercise duration while receiving verapamil instead of placebo, whereas 2 other patients had a slight reduction in exercise time with verapamil.

Control and placebo tests: There were no significant differences between the baseline control test (before the start of the protocol) and the placebo test performed at the end of the 2 week, single-blind phase. Comparison of the placebo tests before the single-blind and double-blind phases, performed approximately 7 to 10 weeks apart, did show a significant increase in exercise duration and a reduction in the rate-pressure product during submaximal exercise during the second test.

Adverse effects: No patient had to be withdrawn from the study because of significant adverse effects. One patient had abnormal liver function at the end of the double-blind phase and was withdrawn from a long-term follow-up study. In 6 of the patients (22%) constipation developed approximately 1 week after starting verapamil, but only 3 of them required treatment with stool softeners. Five patients had a prolongation of the P-R interval by 20 to 40 ms with verapamil, but did not exhibit first-degree heart block. One patient with preexisting first-degree block had no further lengthening of the P-R interval while receiving verapamil. One patient manifested a junctional rhythm, which subsided during treadmill exercise, while taking verapamil.

Discussion

Present study: The results of this study document both subjective and objective improvement in patients with stable angina of effort receiving verapamil, 480 mg per day. Mean anginal attack frequency was decreased 61% and nitroglycerin consumption was reduced 65% compared with the placebo responses during the double-blind phase; the duration of time on a treadmill increased 17%. Verapamil produced few adverse effects; these consisted primarily of constipation, which was remedied by stool softeners or dietary adjustment.

Previous studies (Table I): Six other double-blind, randomized, crossover, placebo-controlled clinical trials have evaluated verapamil therapy in patients with

stable angina of effort. Trials not using such a study design are not considered in this report.

Neumann et al.[14] evaluated verapamil, 120 mg daily for 6 weeks, in 30 nursing home patients (15 men and 15 women) averaging more than 75 years of age. Verapamil significantly decreased the number of nitroglycerin tablets consumed, as compared with a 6 week placebo period.

Phear[15] compared verapamil, 240 mg daily, with placebo in 20 patients (13 men and 17 women, mean age 58 years) with each agent given for 2 weeks. No reduction in the frequency of anginal attacks or nitroglycerin consumption was noted. No buffer period was present between randomization phases, however, and the possibility of lingering verapamil action in some patients subsequently randomized to placebo was not considered.

Andreasen et al.[16] assessed subjective and objective variables in a multicenter Danish study involving 47 patients (38 men and 19 women, aged 48 to 71 years) which compared verapamil, 240 mg daily, with placebo, each given for 4 weeks. Verapamil significantly reduced the frequency of anginal attacks and nitroglycerin tablets consumed. Exercise capacity, assessed from the amount of time required to produce ischemic S-T depression during bicycle ergometry, was significantly enhanced. Adverse effects from verapamil were minimal; only 3 patients reported constipation.

More recent studies have validated the subjective and objective benefits of verapamil in the treatment of effort-induced angina. Bala Subramanian et al.[11] administered verapamil, 360 mg daily, or placebo to 28 patients, 25 men and 3 women, for 2 weeks each, and then treated each patient with open-label verapamil for 4 weeks. Compared with placebo, verapamil significantly increased mean treadmill tolerance by 38% during the double-blind phase, and then by an *additional* 21% during open-label therapy. Verapamil therapy resulted in a significant reduction in anginal attacks (47%) and nitroglycerin consumption (45%) during the double-blind phase of the study. Seven patients had constipation requiring laxative therapy. Two patients had mild first-degree heart block.

Pine et al.[17] compared verapamil with placebo in 30 patients with effort-related angina pectoris who underwent a more detailed evaluation of response. Each patient received verapamil, 240, 360, and 480 mg per day, for 1 week in a single-blind fashion; this was followed by a double-blind placebo-controlled randomized phase in which placebo was compared with verapamil, administered in the dose which produced the greatest improvement in exercise tolerance during the single-blind phase. During the double-blind phase, verapamil significantly reduced the mean anginal attack frequency 47% and nitroglycerin consumption 55%, and significantly increased exercise capacity on the treadmill 42%. Seven patients had adverse reactions (rhythm disturbances in 3 patients, pulmonary edema in 1, and noncardiac symptoms in 3) with 480 mg daily of verapamil, all of which disappeared with a reduction in the dose to 360 mg daily. In these 7 patients the improvement in exercise duration on the lower dose of the drug (360 mg daily) was similar to that observed with the higher dose (480 mg daily).

Tan et al.,[18] in their evaluation of 12 men aged 45 to 73 years, found that verapamil, 320 mg daily for 4 weeks, produced a 78% reduction in anginal attacks and a 20% improvement in exercise duration on a treadmill, when compared with placebo therapy for 4 weeks. The ejection fraction declined from 40 ± 9% (at rest) to 35 ± 11% (at peak effort) during placebo therapy, whereas during verapamil therapy the ejection fraction did not decrease during exercise (44 ± 8% at rest and 45 ± 12% at peak effort).

These 6 studies,[11,14–18] combined with ours,[12] comprise 193 patients treated with verapamil in double-blind, placebo-controlled, randomized protocols; all but 1 study[15] showed significant improvement during treatment with verapamil. The dose of verapamil ranged from 120 to 480 mg daily; adverse effects were infrequent and minor in all but 1 study,[17] in which more frequent adverse reactions were observed when a dose of 480 mg daily was employed. Since 82% of the patients studied were men, it is unclear whether verapamil has similar antianginal effects in women.

In evaluating the efficacy of new antianginal medications, careful attention must be given to the recruitment of patients with stable mechanical and electrical heart function who will be reliable in taking both active drug and placebo pills. Subjective (anginal attack frequency and nitroglycerin consumption) and objective (treadmill performance) measures of drug effect should be evaluated concurrently. Patients selected should have reproducible exercise-induced angina, preferably within 3 to 6 minutes,[19] on a standard exercise protocol in order to avoid distress from leg fatigue or hyperventilation at higher intensities of exercise. In analyzing group patient exercise data, consideration should be given to placebo effects, to training effects during sequential exercise tests,[20,21] and to interpatient variability during control or placebo exercise tests.

In the present protocol, comparison of single and subsequent double-blind placebo tests revealed that the treadmill time increased and the submaximal exercise heart rate and rate-systolic blood pressure product decreased significantly after the patients had completed a minimum of 5 treadmill tests. These changes might have been due to a training effect, since blood verapamil and norverapamil levels measured at the time of the double-blind placebo test were 0 to 18 ng/ml in 24 patients. Such minute amounts of blood verapamil would have been unlikely to reflect lingering drug action on the heart. A further significant increase in treadmill performance induced by verapamil, as compared with placebo, occurred during the double-blind phase of the study. Since training effects, if present, would probably have been completed before the initiation of the double-blind study phase, these results confirmed the exercise-enhancing capacity of verapamil.

In most studies on new antianginal therapy, some patients will respond better than others. Comparison of individual responses may elucidate mechanisms involved in a greater therapeutic response. In our study, 12 patients showed minimal (less than 10%) or no im-

provement in exercise duration while receiving verapamil, compared with placebo, in the double-blind study phase. These 12 patients did not differ from the other 14 patients with respect to baseline anginal frequency or nitroglycerin consumption. However, the mean exercise duration on the initial baseline exercise test before entry into the study was 23% less ($p < 0.05$) in the 14 patients with a therapeutic response to verapamil during the double-blind phase than in patients with minimal responses. These findings indicate that verapamil may confer its greatest benefit on patients whose exercise capacity is most restricted by angina before entry into the study.

Mechanism of verapamil action: In the present study verapamil, compared with placebo, significantly decreased both the resting and submaximal heart rate, the submaximal systolic blood pressure, and the resting and submaximal rate-pressure product during the double-blind phase. We observed a greater effect on heart rate than on systolic blood pressure; other investigators have noted just the opposite.[22] Regardless of which effect predominates, these responses can be explained by the negative chronotropic actions of verapamil,[23,24] as well as its dilating effects on systemic arterioles.[25,26] These findings are consistent with the hypotensive actions of verapamil during rest and bicycle ergometry in patients with essential hypertension.[27]

Clinical implications and perspectives: Thus, verapamil is a safe, effective drug in the treatment of patients with stable exertional angina pectoris. The effective dose ranges from 240 to 480 mg daily in 3 or 4 divided doses. Adverse effects are infrequent and mild, and consist primarily of constipation and prolongation of atrioventricular conduction. Overt congestive heart failure may occur rarely in patients with preserved left ventricular function. Abnormal hepatic function has been reported infrequently after verapamil therapy. In the treatment of angina of effort, verapamil may offer special advantages to patients who also have bronchial asthma or peripheral vascular disease. Such patients are likely to have an exacerbation of these disorders during therapy with beta-adrenergic blocking agents, when these are used in doses required to alleviate exercise-induced angina.[6,7]

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Calcium Channel Blockade as Primary Therapy for Stable Angina Pectoris

A Double-Blind Placebo-Controlled Comparison of Verapamil and Propranolol

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The effectiveness and safety of the beta-adrenergic blocking agent propranolol and the calcium channel antagonist verapamil were compared in 22 patients with chronic stable angina pectoris using a double-blind randomized placebo-controlled crossover protocol. The double-blind phase was preceded by a 2 week single-blind placebo period, followed by randomization to either either 4 weeks' therapy with verapamil, 360 mg/day, or propranolol, 240 mg/day, followed by crossover to the other drug. Both verapamil and propranolol increased exercise tolerance (5.5 ± 0.4 minutes with placebo, 7.8 ± 0.5 minutes with propranolol [$p < 0.001$], and 9.1 ± 0.5 minutes with verapamil [$p < 0.001$]), but the increase with verapamil was significantly greater ($p < 0.01$). Both drugs prolonged the exercise duration to 1 mm S-T depression (3.3 ± 0.4 minutes with placebo, 5.7 ± 0.5 minutes with propranolol [$p < 0.001$] and 5.5 ± 0.6 minutes with verapamil [$p < 0.001$]); the degree of improvement was similar with both active drugs. Both drugs decreased the resting heart rate (76 ± 3 beats/min with placebo, 56 ± 2 beats/min with propranolol [$p < 0.001$], and 71 ± 3 beats/min with verapamil [$p < 0.01$]), but the heart rate decreased more with propranolol than with verapamil ($p < 0.001$). Neither drug produced significant adverse reactions. This study, along with 8 similar double-blind placebo-controlled randomized investigations which have compared verapamil with propranolol, indicate that verapamil is as effective and safe as propranolol in relieving symptoms and improving exercise tolerance in patients with chronic stable angina pectoris and may be considered a first-line therapeutic agent in patients with ischemic heart disease.

Beta-adrenergic blocking drugs are presently the primary therapeutic modality in the management of patients with angina pectoris.[1–6] Although many patients have significant improvement in symptoms after the institution of beta-blocker treatment, these drugs can cause depression and fatigue, prevent recognition of hypoglycemic episodes in insulin-dependent diabetics, and produce clinical deterioration in patients with peripheral vascular disorders and obstructive pulmonary disease.[7] Alternative first-line antianginal therapy is needed for the management of effort-related ischemia in such patients, as well as those who remain symptomatic despite adequate therapy with nitrates and beta-blocking agents.

The development of drugs that block calcium influx into cardiac muscle and vascular smooth muscle has led to the application of such agents in the treatment of angina pectoris.[8–11] Of the available agents, verapamil has been in clinical use almost as long as the beta blockers, and it possesses powerful antianginal properties that provide sustained long-term benefit.[12–15] Verapamil has been shown highly effective in the

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management of patients with angina at rest,[16–18] and it is superior to propranolol in this clinical condition.[19] Verapamil is also highly effective in effort-related angina,[13,20,21] and a number of clinical trials have shown that it is comparable or superior to propranolol in patients with exertional symptoms.[22–30]

The present report details the results of a double-blind placebo-controlled randomized crossover trial comparing verapamil and propranolol in patients with stable effort-related angina pectoris; a preliminary report of these results was published in 1981.[30] Our data are similar to those of 8 other studies[22–29] which have employed a similar double-blind crossover study design; these are also reviewed herein. Together, these data indicate that verapamil is a safe and effective alternative to propranolol in patients with chronic stable angina pectoris and may be a first-line drug for many patients with ischemic heart disease.

Methods

Twenty-five patients with effort-related stable angina pectoris (age range 41 to 69 years, 22 men and 3 women) entered the trial. All patients had chest pain (at least 4 attacks per week) relieved by rest and by sublingual nitroglycerin and at least 1 mm horizontal S-T depression on standardized treadmill exercise testing. Coronary artery disease was confirmed either by coronary arteriography or by the occurrence of a transmural myocardial infarction infarction within the last 12 months.

Patients with a recent myocardial infarction (within the last 4 months), with unstable or accelerating symptoms, with clinical congestive heart failure or resting blood pressure over 160/100 mm Hg, or with insulin-dependent diabetes mellitus were excluded from the trial. No patient received digitalis, diuretics or other cardiovascular agents before or during the study. Any patient showing more than 0.5 mm S-T depression on standing, with hyperventilation or with Valsalva maneuvers, or who failed to develop classic angina on the initial diagnostic treadmill exercise test with at least 1 mm S-T segment depression in both bipolar leads, was not entered into this trial.

Trial design: After an initial 2 week placebo run-in period, all 25 patients were randomized to propranolol, 240 mg daily, or verapamil, 360 mg daily, administered in 3 divided doses for 4 weeks, followed by crossover to the alternate drug. Because 4 weeks elapsed between each exercise test, no washout period was incorporated. All evaluations were repeated at the end of placebo and at 4 and 8 weeks of active drug therapy.

All patients were examined for development of cardiac failure, and side effects were noted in a standard questionnaire. All patients gave informed consent for participation in the trial and the project was approved by the Hospital Ethical Committee.

Exercise testing: All tests were performed using a motor-driven treadmill; the speed and gradient were regularly calibrated and the program (Table I) was governed by a computer (Marquette Computer Assisted System for Exercise). Two bipolar leads (CM5 and CC5) were continuously recorded before, during, and after exercise in a 25:1 compressed format. Digital printouts of S-T depression at the J point, S-T slope, heart rate, and ectopic count were generated for every minute of the test and for a final analog trend plot of each complete test.[31] Systolic blood pressure was measured every 3 minutes and at termination of exercise with a mercury sphygmomanometer.

TABLE I Treadmill Protocol

Stage	Time (min)	Speed (miles/h)	Gradient (% Incline)
1	3	2	0
2	3	4	4
3	3	3	8
4	3	3	12
5	3	3	16
6	3	3	20
7	3	4.5	20

All exercise tests were limited by angina, dyspnea, fatigue, or pain in the legs. All were performed in the morning 90 to 150 minutes after the last dose of drug and after 30 minutes' rest in a temperature-controlled laboratory. The standard safety precautions as recommended by the American Heart Association were followed.[32]

From the computer printouts, we derived the exercise time (time taken to develop angina or fatigue), resting heart rate, maximal heart rate, double product (systolic blood pressure × heart rate/100), and peak S-T depression in CM5. The following variables were calculated from the computer printouts[30,31]: (1) workload = the product of the distance walked in kilometers and the sine angle of the treadmill in degrees, (2) 1 mm time and 2 mm time = time required to produce 1 and 2 mm S-T segment depression in both bipolar leads CM5 and CC5, (3) S-T segment depression at the same workload = the magnitude of S-T segment depression at the maximal workload achieved in each patient during placebo therapy.

Ambulatory monitoring: Continuous ambulatory monitoring of 2 channels of the electrocardiogram (CM5 and CC5) was performed using a frequency-modulated tape recorder with a quartz controlled time channel (Oxford Medilog Mark II) for a minimum of 24 hours.[33] All tapes were visually analyzed for prolongation of the P-R interval or higher degrees of heart block. Mean hourly heart rates were obtained using a computer program. The tapes were then played into a minicomputer which stored minute-averaged values of mean, minimal, and maximal heart rate and S-T segment values for 24 hours in a 5.25 inch floppy disc. Software analysis enabled acquisition of a number of objective variables such as maximal S-T depression, episodes of S-T depression of 1 mm in 24 hours, and the number of minutes in which the heart rate exceeded a preset figure (100 beats/min).

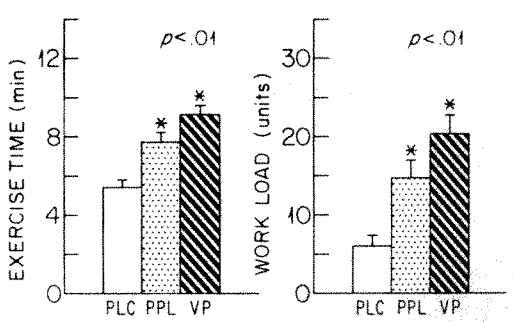

FIGURE 1. Duration of exercise (**left panel**) and workload (**right panel**) during therapy with placebo (PLC), propranolol (PPL), and verapamil (VP). Data are shown as means ± standard error of the mean. **Asterisks** indicate significance of differences between active drug therapy compared with placebo. P values indicate significance of differences between propranolol and verapamil.

TABLE II Comparative Effects of Placebo, Propranolol, and Verapamil in Patients With Chronic Stable Exertional Angina*

	Placebo	Propranolol (240 mg/day)	Verapamil (360 mg/day)	A	B	C
Exercise time (min)	5.5 ± 0.4	7.8 ± 0.5	9.1 ± 0.5	<0.001	<0.001	<0.01
Workload (units)	6.1 ± 1.4	14.8 ± 2.2	20.4 ± 2.4	<0.001	<0.001	<0.01
Resting heart rate (beats/min)	76 ± 3	56 ± 2	71 ± 3	<0.001	<0.01	<0.001
Maximal heart rate (beats/min)	135 ± 3	104 ± 3	130 ± 3	<0.001	NS	<0.001
Double product at peak effort (beats × mm Hg/min)	216 ± 8	164 ± 7	204 ± 6	<0.001	NS	<0.001
1 mm time (min)	3.3 ± 0.4	5.7 ± 0.5	5.5 ± 0.6	<0.001	<0.001	NS
2 mm time (min)	4.3 ± 0.5	7.3 ± 0.7	7.1 ± 0.9	<0.001	<0.001	NS
S-T↓ at peak effort (mm)	2.4 ± 0.2	1.7 ± 0.1	2.2 ± 0.2	<0.01	NS	NS
S-T↓ at same workload as placebo (mm)	2.3 ± 0.2	1.0 ± 0.1	1.3 ± 0.2	<0.001	<0.001	NS
Heart rate at same workload as placebo (beats/min)	131 ± 3	94 ± 3	116 ± 3	<0.001	<0.001	<0.001

* Data are expressed as mean ± standard error of the mean. The 3 columns on the right indicate p values for level of significance of differences between the 3 treatment periods, where A compares placebo with propranolol, B compares placebo with verapamil, and C compares propranolol with verapamil. NS = not significant; S-T↓ = S-T segment depression.

Statistical analysis: Group data are presented as means ± standard error of the mean. Statistical analyses were performed by the *t* test for paired data.

Results

Twenty-two patients (20 men and 2 women) with an age range of 41 to 69 years completed the trial.

Exercise duration (Fig. 1, Table II): The duration of exercise was prolonged by both propranolol ($p < 0.001$) and verapamil ($p < 0.001$), but the improvement seen with verapamil was significantly greater ($p < 0.01$). All 22 patients stopped exercise on the treadmill because of angina during the placebo phase, and 18 stopped the treadmill test because of angina during treatment with propranolol, but only 12 patients had angina during exercise testing with verapamil therapy. The exercise time with verapamil was longer than with propranolol in 17 patients, shorter in 4 patients, and similar in 1 patient. The maximal workload achieved averaged 6.1 ± 1.4 units with placebo, 14.8 ± 2.2 units with propranolol ($p < 0.001$ versus placebo), and 20.4 ± 2.4 units with verapamil ($p < 0.001$ versus placebo and $p < 0.01$ versus propranolol).

Exercise variables and S-T segment responses (Fig. 2, Table II): The time to 1 and 2 mm S-T segment depression during placebo therapy was prolonged similarly by both verapamil and propranolol. At the same workload achieved during placebo therapy, propranolol reduced the magnitude of S-T depression (from 2.3 ± 0.2 mm to 1.0 ± 0.1 mm, $p < 0.001$), which was similar to the reduction seen with verapamil (1.3 ± 0.2 mm, $p < 0.001$). However, the magnitude of S-T depression at maximal exercise was reduced only by propranolol ($p < 0.01$) and not by verapamil; this degree of S-T depression, however, was seen after 9.1 minutes of exercise during verapamil therapy, compared with only 5.5 minutes on placebo. The difference in the effect of the 2 drugs on S-T segment depression at maximal exercise was related to our observation that only propranolol therapy was associated with a significant reduction in double-product at peak effort ($p < 0.001$); this effect was not seen with verapamil.

Compared with placebo (76 ± 3 beats/min), both drugs reduced the resting heart rate (to 56 ± 3 beats/min with propranolol and to 71 ± 3 beats/min with verapamil); however, the effects of propranolol on heart rate were more pronounced ($p < 0.01$). The heart rate at the same workload achieved at peak effort during placebo therapy was reduced by both drugs; again, the effects of propranolol were more pronounced. Propranolol decreased the heart rate during maximal exercise ($p < 0.001$), but verapamil did not.

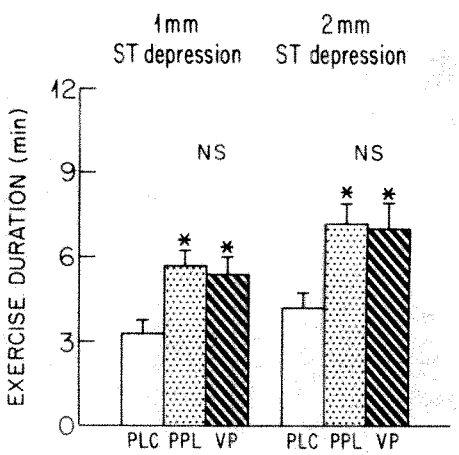

FIGURE 2. Time on a treadmill exercise test to the development of 1 and 2 mm S-T depression during treatment with placebo (PLC), propranolol (PPL), and verapamil (VP). Data are shown as means ± standard error of the mean. **Asterisks** indicate significance of differences between active drug therapy compared with placebo. NS indicates that the differences between propranolol and verapamil therapies were not significant.

TABLE III Double-Blind Placebo-Controlled Randomized Clinical Trials Comparing Verapamil and Propranolol*

Reference	Country & Year	Patients (n)	Duration	Methods	V Daily Dose (mg)	Beta-Blocking Agent & Dose (mg)	Findings
Sandler et al.[22]	UK (1968)	16	4 weeks	1,2	120,360	Propranolol, 300	Both drugs equal at higher dose of V
Liveseley et al.[23]	UK (1973)	32	4 weeks	1,2	240,360	Propranolol, 300	Both drugs equal at higher dose of V
Fagher et al.[24]	Sweden (1977)	13	4 weeks	1,2	240	Practolol, 300	V effective, P was not; trial-abbreviated
Johnson et al.[25]	US (1981)	18	2 weeks	1,2,3,4	320,480	Propranolol, 160 & 320	Both drugs equal at higher doses of V & P
Sadick et al.[26]	Australia (1981)	18	3 weeks	1,2,4	320	Propranolol, 320	Both drugs equal
Leon et al.[27]	US (1981)	11	48 hours	1,2	480	Propranolol, range 160–320	V superior
Frishman et al.[28]	US (1981)	20	4 weeks	1,2	480	Propranolol, 320	V superior
Arnman and Ryden[29]	Sweden (1982)	24	4 weeks	1,2	360	Metoprolol, 200	V superior
Bala Subramanian et al. (present study)	UK (1982)	22	4 weeks	1,2,3	360	Propranolol, 240	V superior

* Duration refers to number of weeks treated with each drug. Methods: 1 = clinical evaluation; 2 = exercise testing; 3 = Holter monitoring; 4 = radionuclide studies. P = propranolol or practolol; UK = United Kingdom; US = United States; V = verapamil; Year = year of publication.

Twenty-four ambulatory monitoring (Fig. 3): The pooled mean hourly heart rate with placebo, verapamil, and propranolol was related to clock time and expressed as a continuous curve (Fig. 3). Both drugs reduced the heart rate throughout the day, but the reduction with propranolol was greater. The total area of S-T depression was calculated for the entire 24 hours and divided by the number of minutes in which S-T depression occurred to yield an average S-T level. The mean S-T depression during placebo (-1.5 ± 0.2 mm) was reduced similarly by propranolol (-0.7 ± 0.2, $p < 0.001$) and by verapamil (-0.9 ± 0.2, $p < 0.001$).

Adverse reactions: Both drugs were well tolerated with few side effects. Constipation was a constant feature with verapamil and tiredness or lethargy with propranolol. Two patients were withdrawn during the propranolol phase because of dyspnea at rest and severe hypotension. One patient had a myocardial infarction and died during the verapamil phase. Autopsy revealed severe triple-vessel disease with total obstruction of the left anterior descending artery. No P-R interval prolongation on the electrocardiogram was observed in any patient during either active drug phase.

Discussion

Results of the present trial: Since beta-adrenergic blocking agents are presently the therapeutic agents of choice in prevention of effort-induced ischemic chest pain,[1–6] any new antianginal agent should be compared with the beta-blocking drugs in order to establish its relative efficacy and safety. The present report indicates that both verapamil and propranolol prolong the duration of exercise before the appearance of ischemic S-T segment depression and anginal pain. Although all patients were limited by chest pain during placebo therapy, 4 patients during propranolol therapy and 10 patients during verapamil therapy failed to develop angina and stopped exercise because of dyspnea or leg fatigue. Propranolol appeared to exert its effects by a reduction in resting heart rate and in the rate-pressure product at peak effort; hence, the drug reduced the major determinants of myocardial oxygen consumption and, accordingly, reduced the maximal S-T segment depression achieved with exertion. Verapamil produced moderate reductions in heart rate at rest and at submaximal workloads, but it did not decrease the rate-pressure product or the magnitude of S-T segment depression at peak effort. Thus, the drug *delayed* the appearance of but did not attenuate the magnitude of the major determinants of myocardial oxygen demand.

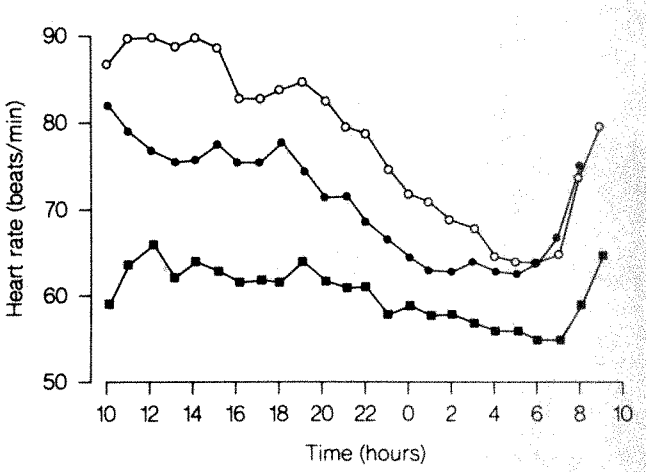

FIGURE 3. Twenty-four hour mean hourly heart rates for 22 patients on placebo, propranolol, 240 mg daily, and verapamil, 360 mg daily. Placebo therapy is indicated by **open circles,** propranolol therapy by **closed squares,** and verapamil therapy by **closed circles.** The **horizontal axis** shows clock time and the vertical axis indicates heart rate. Note the marked and consistent bradycardia produced by propranolol and the milder reduction in heart rate with verapamil.

Recent evidence suggests that these hemodynamic effects are the result of a complex interaction of verapamil's actions on systemic and coronary vessels.[34] Using the fixed doses employed in the present study, verapamil was superior to propranolol in prolonging exercise tolerance in patients with effort-related ischemic symptoms.

Comparison with previous placebo-controlled comparative studies: There have been 9 double-blind placebo-controlled randomized crossover clinical trials comparing verapamil with propranolol; this includes the results of the present trial (Table III). All trials evaluated the improvement in ischemia by both subjective (relief of anginal attacks and reduction of nitroglycerin consumption) and objective methods (exercise testing and, in some cases, Holter monitoring). All but 1 trial used fixed doses of both drugs; in some trials, 2 dose levels of 1 or both drugs were compared. Trials not utilizing a placebo-controlled double-blind design with objective end points are not considered in this report.

Sandler et al.[22] compared 4 weeks' therapy with verapamil in 2 dose levels (120 mg and 360 mg daily) with propranolol, 300 mg daily, in 16 patients with chronic stable angina pectoris. Only the higher dose of verapamil produced subjective and objective improvement in these patients; this was similar to that seen with propranolol. Liveseley et al.[23] compared 4 weeks' therapy with verapamil in 2 dose levels (240 mg and 360 mg daily) with propranolol (300 mg daily) and isosorbide dinitrate (60 mg daily) in 32 patients. The higher dose level of verapamil was similar to propranolol in relieving angina and in prolonging the duration of exercise; both agents were superior to low doses of verapamil and to nitrates. Fagher et al.[24] compared verapamil, 240 mg daily, to practolol, 300 mg daily, in a trial abbreviated because of reports of long-term toxicity with practolol. Although there was some benefit from therapy with verapamil (but not from practolol), the numbers of patients were too small to reach comparative conclusions.

Johnson et al.[25] compared 2 weeks of verapamil therapy to 2 weeks of propranolol therapy in 18 patients with effort-related angina pectoris. Each drug was given at 2 dose levels, each for 1 week: verapamil, 320 and 480 mg, and propranolol, 160 and 320 mg, and patients were evaluated by history, exercise testing, Holter monitoring, and radionuclide evaluation of ventricular function. The higher doses of both drugs attenuated the magnitude of S-T depression seen with exercise testing at a fixed workload, but verapamil was superior to propranolol in reducing the number of nitroglycerin tablets consumed and in reducing the number of episodes of S-T segment deviation on Holter monitoring. Neither drug produced clinically significant depression of left ventricular performance; propranolol caused a deterioration of pulmonary function, but verapamil did not. Sadick et al.[26] recently confirmed these findings; they compared 3 weeks of therapy with verapamil, 320 mg daily, to propranolol, 320 mg daily, in an independent study of 18 patients. Both drugs were equally effective in prolonging exercise tolerance; both drugs caused mild *decreases* in radionuclide ejection fraction at rest but mild *increases* in ejection fraction on effort.

Three recent studies found verapamil superior to propranolol in improving exercise tolerance in patients with angina of effort. Leon et al.[27] compared the efficacy of verapamil in a dose of 480 mg per day with doses of propranolol, 160 to 320 mg/day, individually titrated to produce an optimal clinical response. Verapamil was more effective than propranolol in increasing exercise time; however, patients were selected for this trial because they remained symptomatic on beta-blocker therapy; thus these investigators probably evaluated a patient population that was relatively resistant to propranolol. Frishman et al.[28] compared increasing doses of verapamil, 240, 320, and 480 mg daily, and propranolol, 60, 160, and 320 mg daily, in 20 patients with stable angina of effort; both drugs produced comparable relief of anginal symptoms and both agents increased exercise duration, but the improvement in exercise tolerance was greater with verapamil. Arnman and Ryden[29] compared verapamil, 360 mg daily, with metoprolol, 320 mg daily, in 24 patients; again, verapamil was superior to propranolol in improving exercise tolerance.

Clinical implications and conclusions: As a result, there is overwhelming evidence that verapamil produces subjective and objective relief of effort-related anginal symptoms in patients with ischemic heart disease to a degree comparable to that seen with beta-blocking agents. Although in many of these trials the duration of exercise was increased to a greater degree with verapamil than with propranolol, the differences between the two drugs were small. Furthermore, since all of the reviewed trials (except one) used a fixed-dose regimen for both agents, the greater effects seen with verapamil in some trials may have been abolished had the doses of the beta-blocking agent in these studies been individually titrated. Consequently, it is difficult to conclude that verapamil is superior to propranolol in patients with effort-related symptoms. Some patients clearly preferred and/or benefitted from one drug over the other, and their preference or benefit could not be predicted before a therapeutic trial with each agent. Hence, it is likely that the choice of a first-line agent for a given patient with ischemic heart disease will be dictated by considerations other than drug effectiveness, that is, by contraindications that exist before therapy or by adverse reactions that result after a therapeutic trial with a specific agent.

In conclusion, these results confirm that verapamil is comparable in efficacy to beta-adrenergic blocking drugs in the treatment of chronic stable angina; both agents are well tolerated, and neither significantly affects left ventricular performance.

Acknowledgment

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Comparison of Oral Propranolol and Verapamil for Combined Systemic Hypertension and Angina Pectoris

A Placebo-Controlled Double-Blind Randomized Crossover Trial

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The relative efficacies of oral verapamil, a calcium-entry blocking drug, and propranolol, a beta-adrenergic blocking drug, were compared in 12 patients who had both stable angina pectoris and mild to moderate systemic hypertension, using a placebo-controlled, double-blind, randomized crossover protocol. Compared with placebo, both propranolol and verapamil decreased the frequency of anginal attacks and the number of nitroglycerin tablets consumed, and increased exercise duration and total work; there were no significant differences in the antianginal effect of the two drugs. Both verapamil and propranolol reduced the supine and standing systolic and diastolic blood pressure measured at rest; compared with propranolol, however, verapamil had greater effects on standing diastolic blood pressure ($p < 0.002$). Resting heart rate was reduced from placebo baseline with large doses of both drugs; compared with verapamil, however, propranolol exerted greater effects on resting heart rate and rate-pressure product. Plasma renin activity was increased from placebo baseline with verapamil ($p < 0.05$), but was reduced with propranolol ($p < 0.05$); no significant change in plasma aldosterone was seen with either drug. Verapamil appears to be a safe and effective treatment alternative to propranolol for relieving anginal symptoms, improving exercise tolerance, and reducing elevated systemic blood pressure in patients with both angina pectoris and mild to moderate systemic hypertension.

Verapamil is a calcium-channel blocking drug which has proved useful in the treatment of patients with supraventricular tachyarrhythmias,[1,2] angina pectoris of effort,[3–5] vasospastic angina,[6–8] and hypertrophic cardiomyopathy.[9] Experimental and clinical studies have documented that verapamil can dilate the coronary and peripheral arteries by interfering directly with transmembrane calcium flux.[10] Such systemic vasodilating effects are likely responsible for the effectiveness of the drug in effort-related angina[4]; however, these effects on peripheral resistance suggest that verapamil and other calcium-entry blockers may also be effective in the management of patients with systemic arterial hypertension.[11]

Intravenous verapamil and sublingual nifedipine produce prompt and profound decreases in systemic blood pressure, and thus may be useful in the rapid treatment of hypertensive crises.[12,13] Long-term oral verapamil produces sustained antihypertensive responses in patients with established systemic hypertension.[14–19] However, few studies have compared verapamil with other antihypertensive agents,[15] and no studies have evaluated its efficacy in patients with both hypertension *and* angina pectoris.

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TABLE I Baseline Clinical Data on 12 Patients

Case	Age (yr) & Sex	Angina Attacks/ Week	Prior MI	Baseline Exercise Stress Test*		Coronary Disease on Angiography (>75% Luminal Narrowing)	3 Minute Baseline Standing BP*
				Anginal Pain End Point	S-T↓ (mm)		
1	69M	9	No	No	4.2	Not done	190/108
2	54M	2	Yes	Yes	2.5	Not done	140/92
3	54M	22	Yes	Yes	1.0	3 vessel	144/100
4	68M	5	No	No	5.0	3 vessel	170/108
5	61M	22	No	Yes	2.0	Not done	135/90
6	57M	37	No	Yes	1.5	Not done	142/100
7	61M	17	Yes	Yes	1.0	Not done	150/100
8	53F	13	No	Yes	2.0	3 vessel	150/106
9	51M	14	No	Yes	1.0	3 vessel	150/100
10	64M	4	No	No	1.5	3 vessel	200/108
11	55M	3	No	Yes	3.5	Not done	130/94
12	42M	4	No	Yes	4.0	Not done	150/98

* Value after 2 weeks of placebo treatment.
BP = blood pressure (mm Hg); MI = myocardial infarction; S-T↓ = S-T segment depression (mm).

Since propranolol, a beta-adrenergic blocking drug, is widely used in the management of patients with systemic hypertenstion and with angina pectoris,[20] a comparison of verapamil and propranolol is in order. Accordingly, using data obtained from a previous placebo-controlled, double-blind, randomized crossover trial,[4] we compared the antihypertensive and antianginal effects of verapamil and propranolol in a group of patients with both stable angina pectoris and systemic arterial hypertension.

Methods

Patient selection: Twelve ambulatory patients (11 men and 1 woman) with stable angina pectoris and mild to moderate systemic hypertension were entered into the study after written and informed consent was obtained. The patients represented a subgroup from a previously reported trial,[4] and their characteristics are shown in Table I. The mean patient age was 57.4 years (range 42 to 69). The diagnosis of angina pectoris was established by clinical history (at least 3 attacks/week of angina of effort for 3 months with no evidence of an accelerated course), response to nitroglycerin, and the development of typical symptoms with exercise testing. In addition, each patient demonstrated an abnormal response on two occasions to a standardized, multistage, treadmill exercise test, with at least 1 mm of flat or downward sloping S-T segment depression, 0.08 second after the J point. The diagnosis of coronary artery disease was made on the basis of coronary angiography (75% luminal narrowing of at least 1 major coronary vessel) in 5 patients, previous myocardial infarction in 3 patients, and an ischemic electrocardiographic response to exercise in the other 4 patients. No patient had previous coronary artery bypass surgery.

Systemic hypertension was documented in all patients by an average 3 minute standing diastolic blood pressure of 90 to 110 mm Hg (using Korotkoff phase V) on at least two separate outpatient visits while the patient was receiving no treatment.

Experimental design: During the study, patients were permitted sublingual nitroglycerin tablets (0.6 mg) as the only antianginal medication other than the test drugs. Nitroglycerin tablets were used as needed to treat anginal episodes and were not used prophylactically. Digitalis, propranolol, long-acting nitrates, and antiarrhythmic drugs were withdrawn at least 2 weeks before study entry. Patients received no additional antihypertensive therapy during the trial.

The blinded protocol (Fig. 1) consisted of an initial 2 week single-blind placebo run-in period.[4] During this time each patient received a placebo verapamil tablet (identical to an 80 mg tablet) and a placebo propranolol capsule (identical to an opaque gelatin capsule used throughout the study) every 8 hours. Patients who fulfilled all the inclusion criteria at the end of the second placebo run-in week entered the first drug treatment phase. During this phase, each patient received weekly increasing doses of either verapamil (240 mg/day, 80 mg every 8 hours; 320 mg/day, 80 mg every 6 hours; 480 mg/day, 120 mg every 6 hours) or propranolol (60 mg/day, 20 mg every 8 hours; 160 mg/day, 40 mg every 6 hours; 320 mg/day, 80 mg every 6 hours) over a 3 week titration period. After the

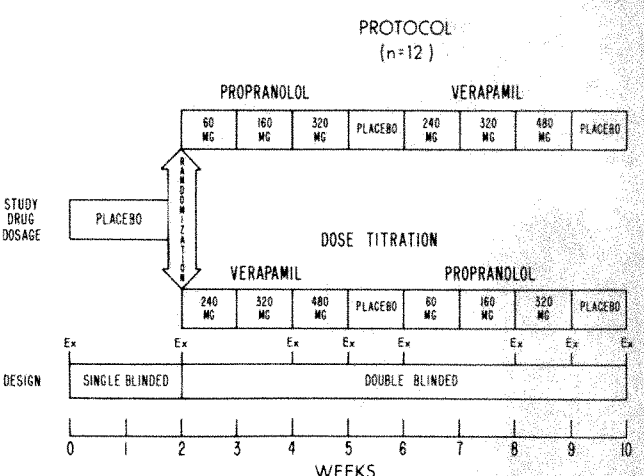

FIGURE 1. Propranolol-verapamil study design: a 2 week single-blind placebo phase, a double-blind randomization into propranolol and verapamil treatment groups, and a 3 week dose-titration phase. After a 1 week withdrawal schedule onto placebo, patients were crossed over to the other treatment schedule for a 3 week dose-titration phase, followed by a 1 week withdrawal schedule onto placebo. Standardized multistage graded exercise tests were performed at the times indicated by **Ex.** Study drug doses are indicated for the dose-titration phases.

TABLE II Effects of Placebo, Propranolol, and Verapamil on Resting Heart Rate and Blood Pressure (BP) in Patients With Angina Pectoris and Hypertension

	Baseline (Placebo)	Propranolol (320 mg/day)	Verapamil (480 mg/day)	Statistical Significance: Placebo vs Propranolol	Statistical Significance: Placebo vs Verapamil	Statistical Significance: Propranolol vs Verapamil
Supine						
Heart rate (beats/min)	80.0 ± 14.2	61.8 ± 7.3	71.6 ± 10.2	p <0.05	NS	p <0.02
Systolic BP (mm Hg)	158.3 ± 26.6	138.0 ± 17.7	144.3 ± 21.0	p <0.05	NS	NS
Diastolic BP (mm Hg)	97.5 ± 6.3	84.5 ± 10.8	87.9 ± 9.4	p <0.05	p <0.05	NS
Rate-pressure product × 10^2 (beats × mm Hg/min)	125.6 ± 25.1	85.0 ± 12.4	103.5 ± 21.4	p <0.05	p <0.05	p <0.01
3 minute standing						
Heart rate (beats/min)	89.7 ± 18.1	63.9 ± 9.7	77.6 ± 10.8	p <0.01	p <0.05	p <0.001
Systolic BP (mm Hg)	154.3 ± 21.5	139.0 ± 23.2	138.7 ± 19.9	NS	NS	NS
Diastolic BP (mm Hg)	100.3 ± 6.3	93.8 ± 11.3	86.6 ± 11.7	NS	p <0.05	p <0.002
Rate-pressure product (beats × mm Hg/min)	137.2 ± 27.0	88.9 ± 19.6	107.7 ± 21.7	p <0.01	p <0.05	p <0.001

NS = not significant.

initial dose titration, the patients underwent a 3 day down-titration phase, during which the amount of medication was decreased approximately 33% per day. The patients then entered a 5 to 7 day placebo period. After completion of this second placebo period, each patient crossed over to the other medication regimen and the dose titration, down-titration, and placebo phases were repeated.

Clinical observations: All patients kept a detailed daily record of anginal attacks and nitroglycerin tablets consumed. Blood pressure and heart rate determinations were made weekly at the same time of the day, 1 to 2 hours after ingestion of placebo or the experimental durg, which is the time of peak pharmacologic activity of propranolol and verapamil.[21]

Exercise tests: Each patient underwent serial exercise tests at visits 1, 2, 4, 5, 6, 8, 9, and 10 (Fig. 1); data from all visits except visit 1 were used for analysis. Multistage treadmill exercise testing consisted of identical sequential 3 minute stages of increasing workload, speed, and elevation using the Bruce protocol.[22] Tests were performed at approximately the same time and same day of the week for each patient. All patients were in the postabsorptive state and had ingested all study medication 1.0 to 2.5 hours before each test.

During exercise, blood pressure was measured every 3 minutes and lead V_5 was continuously monitored on an oscilloscope. The end point of exercise was the onset of angina, severe S-T segment changes of 4 mm or greater in the absence of anginal pain, a significant decrease in systolic blood pressure during exercise, the development of severe ventricular dysrhythmia (3 consecutive premature ventricular complexes), the occurrence of left bundle branch block, or a high degree of atrioventricular block.

Measurements of heart rate, systolic and diastolic blood pressure, S-T segment displacement, arrhythmia, and rate-pressure product (systolic blood pressure × heart rate) were taken at the last minute of each stage of exercise. At the end point of exercise, each test was also analyzed for the maximal

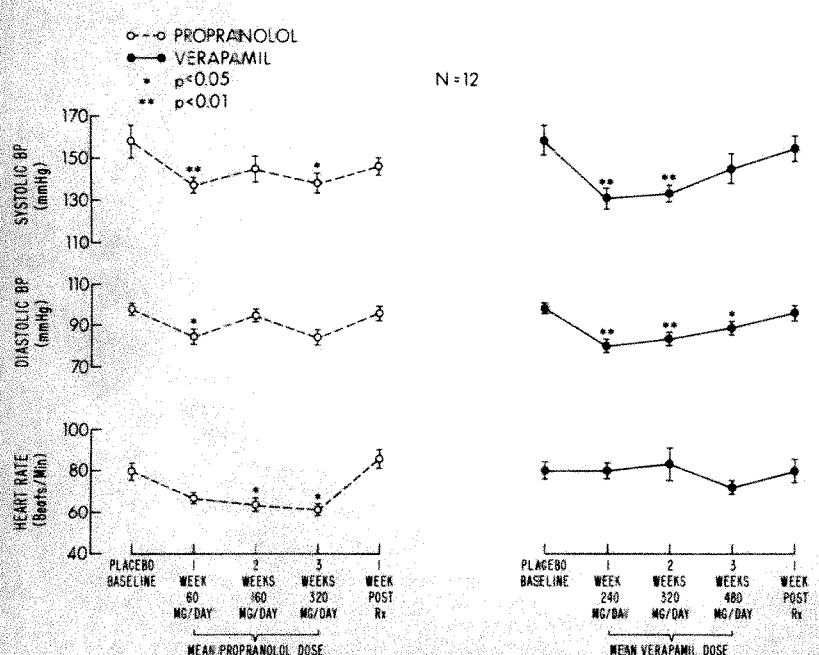

FIGURE 2. Supine blood pressure (BP) and heart rate at rest before, during, and after treatment with increasing doses of oral propranolol and verapamil. Comparisons are made with placebo baseline. Data are shown as mean ± standard error of the mean. Rx = treatment.

heart rate, systolic blood pressure and rate-pressure product achieved, total exercise duration (seconds), S-T segment displacement (mm), and reason for exercise limitation. The exercise work, expressed in kilopond-meters (kpm) was calculated from the formula: Work (kpm) = sin α × speed (m/s) × body weight (kg) × exercise time (seconds) divided by 10^3, where α is the angle of inclination of the treadmill.

Echocardiographic methods: Serial M-mode echocardiography was performed in the supine position in each patient, using a Picker echocardiograph (model 80 C) and a 2.25 MHz 13 mm diameter transducer. The transducer location and examination position were kept constant in all patients, allowing serial comparisons.

The left ventricular end-diastolic (LVd) and end-systolic (LVs) dimensions were measured at the Q wave of the electrocardiogram and at the time of minimal left ventricular diameter, respectively. Care was taken to assess these indexes at the maximal left ventricular dimension recorded and in a consistent relation to mitral valve landmarks. Left ventricular (LV) ejection time was taken as the interval from the Q wave to left ventricular end-systole minus 50 ms. Left ventricular volumes were calculated according to the method of Teichholz et al.[23] The ejection fraction was obtained by subtracting the end-systolic from the end-diastolic volume and dividing this value by the end-diastolic volume. The velocity of circumferential fiber shortening (Vcf) was calculated as (LVd − LVs)/(LVd × LV ejection time).

Plasma renin activity and aldosterone: Peripheral blood was obtained for measurement of plasma renin activity and plasma aldosterone during placebo therapy (visit 2) and during the highest dose levels of both verapamil (visit 5 or 9) and propranolol (visit 5 or 9). Blood was obtained, after an overnight fast, through an indwelling peripheral catheter after the patient had been upright for 2 hours. The samples were withdrawn into a chilled tube of ethylenediamine tetraacetic acid (EDTA). Plasma renin activity was determined by radioimmunoassay using the angiotensin II Immutope kit (Squibb). Plasma aldosterone levels were determined by radioimmunoassay using the aldosterone radioimmunoassay kit (International CIS). Twenty-four hour urinary collections were obtained for total volume, sodium, and potassium at the time of the plasma renin and plasma aldosterone determinations.

Propranolol, verapamil, and norverapamil levels: Blood for propranolol, verapamil, and norverapamil levels were obtained at weekly intervals during the placebo propranolol treatment, verapamil treatment, and drug withdrawal periods. The concentrations of propranolol in plasma were measured using the method of Coltart and Shand.[24] Verapamil and norverapamil levels were measured by liquid chromatographic analysis using the method of Harapat and Kates.[25]

Statistical analysis: Group data are expressed as mean ± standard deviation in the text and as mean ± standard error of the mean in the figures. In comparing the effects of each drug at different doses with placebo baseline values, a modified Fisher least significant difference test was employed. In comparing the effects of verapamil and propranolol, significance was determined for all variables (except renin and aldosterone) based on the difference from baseline values; a two-way analysis of variance was then used to determine whether there was a significant difference between the effects of the drugs. For renin and aldosterone data, because of the large variability of the data, a nonparametric sign test was used. Differences were considered significant if the p value was less than 0.05.

Results

Dropouts and drug compliance: All 12 patients who entered the study completed the trial and were titrated to dose levels of 320 mg/day of propranolol and 480 mg/day of verapamil. Drug compliance (determined by medication counts) for the 3 placebo phases and the 2 drug treatment phases was 95 ± 12%. Plasma drug levels also confirmed patient compliance since a linear relation was seen between dose and plasma level as the drug dose was increased.

Effects on resting blood pressure and heart rate (Table II, Figs. 2 and 3): Verapamil therapy caused a significant reduction from placebo to baseline in supine and standing systolic blood pressure with 320 mg daily

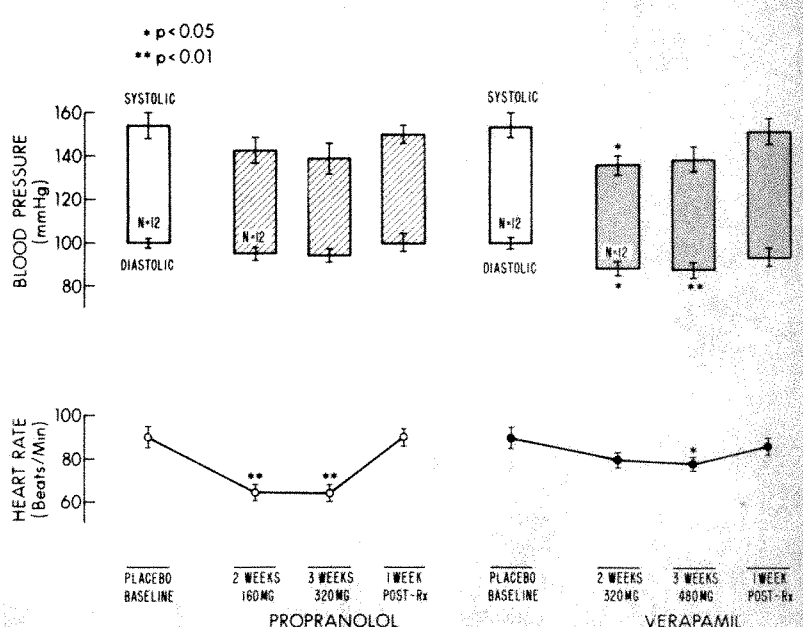

FIGURE 3. Standing blood pressure and heart rate at rest before, during, and after treatment with increasing doses of oral propranolol and verapamil. Comparisons are made with placebo baseline. Data are shown as mean ± standard error at the mean. Rx = treatment.

TABLE III Effects of Placebo, Propranolol, and Verapamil on Anginal Symptoms, Exercise Tolerance, and Exercise Variables

	Baseline (Placebo)	Propranolol (320 mg/day)	Verapamil (480 mg/day)	Statistical Significance: Placebo vs Propranolol	Placebo vs Verapamil	Propranolol vs Verapamil
Angina results						
Attacks/week	12.7 ± 10.5	4.2 ± 6.6	2.0 ± 2.0	$p < 0.01$	$p < 0.01$	NS
NTG consumption/week	8.6 ± 14.4	1.9 ± 4.3	0.9 ± 1.7	NS	NS	NS
Stress test results						
Exercise duration (s)	318.5 ± 113.0	454.1 ± 127.6	485.4 ± 137.4	$p < 0.05$	$p < 0.01$	$p < 0.04$
Exercise work (kpm/10^3)	2.6 ± 1.5	4.6 ± 2.4	5.1 ± 2.6	$p < 0.05$	$p < 0.01$	NS
S-T↓ at end-exercise (mm)	−2.2 ± 1.3	−1.8 ± 1.8	−1.6 ± 1.2	NS	NS	NS
Peak systolic BP (mm Hg)	186.6 ± 27.1	158.9 ± 25.1	166.2 ± 24.5	$p < 0.05$	NS	NS
Peak diastolic BP (mm Hg)	105.2 ± 10.3	94.5 ± 13.9	94.0 ± 13.2	NS	NS	NS
Peak heart rate (beats/min)	137.2 ± 16.9	106.8 ± 13.3	129.7 ± 19.0	$p < 0.01$	NS	$p < 0.001$
Peak rate-pressure product × 10^2 (beats × mm Hg/min)	257.5 ± 52.2	178.6 ± 47.6	215.5 ± 46.0	$p < 0.01$	NS	$p < 0.001$
Inhibition of rate-pressure product × 10^2 (beats × mm Hg/min)						
Change from rest to end-stage I (n = 12)	71.3 ± 18.5	41.3 ± 18.0	43.6 ± 23.4	$p < 0.05$	$p < 0.05$	NS
Change from rest to end-stage II (n = 7)	121.6 ± 15.6	65.8 ± 23.8	79.4 ± 28.1	$p < 0.05$	NS	NS

BP = blood pressure; NS = not significant; NTG = nitroglycerin; S-T↓ = S-T segment depression.

of the drug ($p < 0.01$) but not with 480 mg daily; a dose of 240 mg daily reduced supine systolic pressure ($p < 0.01$) without affecting standing pressure. Verapamil reduced supine and standing diastolic blood pressure at all dose levels ($p < 0.01$ and $p < 0.05$). The best overall blood pressure-lowering effect occurred with 320 mg of verapamil daily, although some patients responded best with higher and lower doses.

Propranolol treatment caused an insignificant reduction from placebo baseline in standing systolic and diastolic blood pressure at all dose levels, but a significant reduction in supine systolic ($p < 0.01$) and diastolic pressure ($p < 0.05$) with 60 mg/day; only supine systolic blood pressure was significantly reduced by 320 mg daily of propranolol ($p < 0.05$). The hypotensive effects of the two drugs did not differ significantly; verapamil, however, produced a greater reduction in standing diastolic blood pressure than did propranolol ($p < 0.002$).

In this study, normalization of blood pressure was defined as a standing diastolic blood pressure of less than 90 mm Hg that was also reduced by at least 10 mm Hg from the baseline value. Eleven of 12 patients had normalization of blood pressure on verapamil, and 7 of 12 responded to propranolol.

Verapamil caused a significant reduction in heart rate only at the highest dose, 480 mg/day, and only for standing heart rate, $p < 0.05$. Propranolol caused a significant reduction in both supine and standing heart rates at the 160 mg and 320 mg/day doses ($p < 0.05$ and $p < 0.01$, respectively). The effects of propranolol on heart rate were more pronounced than those seen with verapamil (supine heart rate, $p < 0.02$; standing heart rate, $p < 0.001$).

Effects on exercise variables (Table III, Fig. 4): The change in rate-pressure product from rest to stage I was significantly reduced by both propranolol and verapamil (both $p < 0.05$); the change in rate-pressure

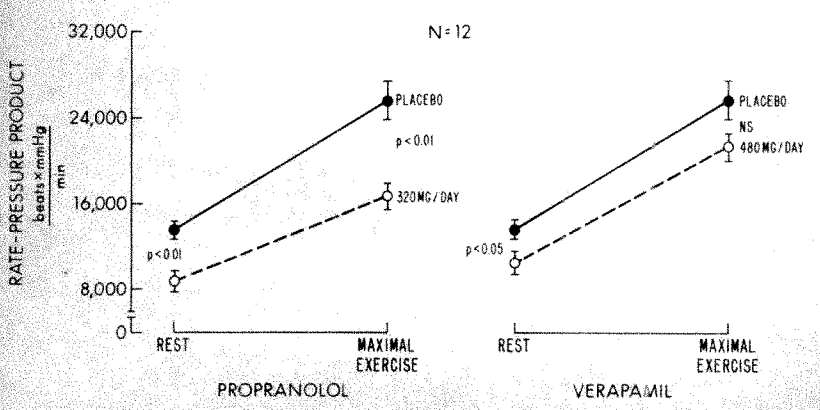

FIGURE 4. Comparative effects of placebo, propranolol, and verapamil on rate-pressure product at rest and during maximal exercise. **Solid lines** indicate placebo therapy; **dashed lines** indicate the effects of active drug therapy. Values are mean ± standard error of the mean. NS = not significant.

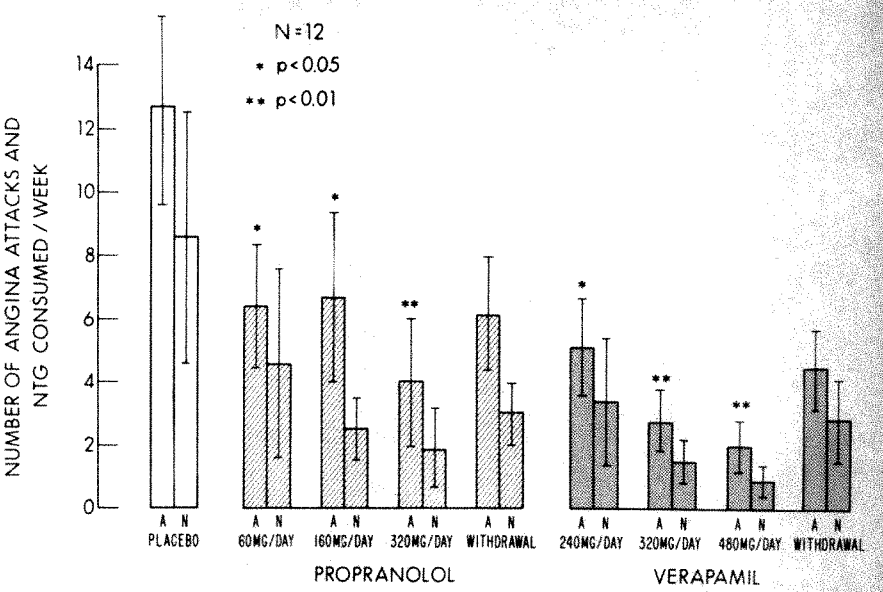

FIGURE 5. Weekly frequency of angina pectoris attacks (A) and nitroglycerin (NTG) consumption (N) before, during, and after treatment with increasing doses of oral propranolol and verapamil. Comparisons are made with placebo baseline. Data are shown as mean ± standard error of the mean.

product from rest to stage II was reduced only by propranolol ($p < 0.05$) and not by verapamil. At maximal exercise, heart rate, systolic blood pressure, and rate-pressure product were significantly lower with propranolol ($p < 0.01$), but these variables were not affected by verapamil; the changes seen with propranolol were significantly greater than those seen with verapamil ($p < 0.01$).

Effects on angina pectoris and exercise-induced ischemia (Table III, Fig. 5): There was a significant reduction in the number of anginal attacks per week reported in patient diaries with both drugs at all dose levels. The optimal antianginal effects appeared at the highest dose levels of both drugs; there was no difference in the magnitude of improvement in angina seen with verapamil and propranolol.

Verapamil and propranolol did not reduce the magnitude of S-T segment depression at maximal exercise seen during placebo therapy. At submaximal exercise, despite a higher rate-pressure product with verapamil than with propranolol, the degree of S-T segment depression was greater with propranolol than with verapamil.

Four patients demonstrated an arrhythmia during the placebo baseline exercise test: 2 patients had unifocal premature ventricular complexes during exercise that were eliminated by propranolol and verapamil but returned upon withdrawal of both drugs, 1 patient had frequent premature ventricular complexes and ventricular bigeminy during exercise that were not affected by either propranolol or verapamil, and 1 had frequent atrial premature contractions that were completely eliminated by propranolol and verapamil treatment. No patient manifested new or enhanced arrhythmias while receiving verapamil and propranolol.

Exercise tolerance (Table III, Fig. 6): Significant increases in total exercise time and calculated exercise work were demonstrated with both propranolol (160 and 320 mg/day) and verapamil treatment (320 and 480 mg/day). The mean overall improvement was greatest at the highest dose levels. Verapamil was more effective in improving exercise time than propranolol ($p < 0.04$).

Effects on echocardiographic indexes of left ventricular function (Table IV): Neither drug altered end-diastolic or end-systolic volumes, ejection fraction, or the velocity of circumferential fiber shortening.

Plasma drug levels: There was a linear relation between the plasma level of propranolol and the drug dose ($r = 0.60$). The plasma concentrations found after 60, 160, and 320 mg of propranolol/day were 33.4 ± 39.9, 84.7 ± 69.4, and 162.7 ± 98.3 ng/ml, respectively. There was also a linear relation between drug dose and the plasma levels of verapamil and its active metabolite, norverapamil ($r = 0.54$, $r = 0.52$). The concentrations found after 240, 320, and 480 mg/day of verapamil were

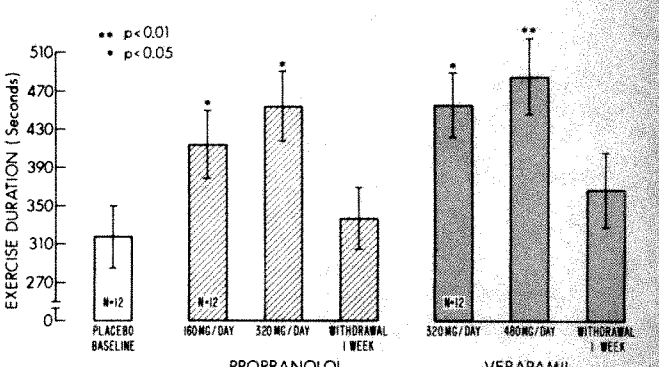

FIGURE 6. Treadmill exercise duration before, during, and after treatment with increasing doses of oral propranolol and verapamil. Comparisons are made with placebo baseline. Values are shown as mean ± standard error of the mean.

TABLE IV Effects of Placebo, Propranolol, and Verapamil on Echocardiographic Indexes of Left Ventricular Function

	Placebo	Propranolol (320 mg/day)	Verapamil (480 mg/day)
End-diastolic volume index (ml/m^2)	64.9 ± 14.5	69.2 ± 18.7	68.9 ± 16.2
End-systolic volume index (ml/m^2)	29.8 ± 15.3	29.8 ± 12.2	30.3 ± 15.1
Ejection fraction (%)	56.1 ± 14.7	58.0 ± 9.0	57.9 ± 12.7
Velocity of circumferential fiber shortening (circ/s)	1.03 ± 0.26	0.96 ± 0.20	1.03 ± 0.24

141.5 ± 82.4, 218.8 ± 129.7, and 315.9 ± 107.7 ng/ml, respectively; for norverapamil, 136.6 ± 50.4, 179.9 ± 70.2, and 252.7 ± 57.9, respectively. There was no relation between plasma drug levels of propranolol or verapamil and clinical responses to these drugs (blood pressure- and heart rate-lowering effects, effects on exercise tolerance, reduction in anginal attacks).

Plasma renin and aldosterone levels (Fig. 7): Compared with placebo (111.4 ± 128.7 ng/100 ml/h), plasma renin activity was significantly reduced by propranolol (56.9 ± 117.8 ng/100 ml/h, $p < 0.05$), but increased during treatment with verapamil (291.3 ± 338.7 ng/100 ml/h, $p < 0.05$); the effects of the two drugs on plasma renin activity differed significantly ($p < 0.01$). There was no relation between the changes in plasma renin activity with propranolol or verapamil and the magnitude of the decrease in blood pressure seen with the two drugs. There were no significant differences from placebo with verapamil or propranolol in the concentration of sodium or potassium excreted in the urine over 24 hours. Mean plasma aldosterone levels decreased slightly but not significantly with propranolol and increased, but not significantly, with verapamil (186.8 ± 96.9 pg/ml with placebo, 161.2 ± 110.9 pg/ml with propranolol, and 291.3 ± 338.7 pg/ml with verapamil).

Safety variables: No changes in body weight were noted with either verapamil or propranolol therapy. One patient complained of fatigue on propranolol, and another patient had constipation with verapamil. All routine screening blood tests, urinalyses, electrocardiograms (P-R intervals), and chest x-ray films remained unchanged during the study.

Discussion

Antihypertensive effects of verapamil: Although most of the interest surrounding the calcium-channel blocking drugs has centered on their use in the management of patients with angina pectoris[3–8] and supraventricular tachyarrhythmias,[1,2] these agents are also effective in the management of patients with hypertension.[11,26,27] Earlier experience with calcium antagonists in such patients focused on their parenteral use in hypertensive crises.[13,26,27] More recently, oral therapy with verapamil, nifedipine, and diltiazem has been reported to produce short-term decreases in systemic pressure in hypertensive patients[14–19,28,29]; the doses of verapamil used in these studies have ranged from 80 to 160 mg orally 3 or 4 times daily. However, there have been few studies comparing the effectivensss of verapamil with that of other antihypertensive agents.[15,30]

The results of this double-blind, placebo-controlled study demonstrate that verapamil is an effective antihypertensive agent in patients with both hypertension and angina pectoris. The drug significantly reduced resting systolic and diastolic blood pressure in the standing and supine positions at the lowest (240 mg/day) and highest doses (480 mg/day), but its greatest hypotensive effects were observed with 320 mg daily. The explanation for this partial loss of effectiveness with the highest verapamil dose is not known, but may be related to the partial development of drug tolerance (since doses of the drug were administered in an incremental sequence) or to the activation of counteractive forces (that is, the renin-angiotensin or sympathetic nervous system) with higher doses of verapamil, which may not occur with lower doses. Although propranolol also effectively lowered blood pressure in this study, verapamil was more effective in reducing standing diastolic blood pressure at rest. Postural hypotensive responses were not seen with either drug. Eleven of 12 patients had normalization of blood pressure with verapamil; 7 of 12 patients responded to propranolol.

Mechanism of hypotensive effects: The mechanisms underlying verapamil's antihypertensive effects are likely to be multifactorial. The drug is a potent peripheral vasodilator agent and therefore exerts hypotensive actions similar to those seen with other direct-acting vasodilator drugs. Therapy with most vasodilator agents is accompanied by sympathetically mediated reflex increases in heart rate and cardiac output, which tend to diminish their antihypertensive effectiveness and are often responsible for producing many of their adverse effects.[31] However, increases in heart rate and cardiac output do not generally accompany verapamil treatment[12] because the drug exerts direct depressant effects on sinoatrial automaticity and myocardial contractility.[32] Hence, the inherent limitations of traditional vasodilator therapy in the management of patients with systemic hypertension are not seen with verapamil. The mechanisms underlying verapamil's antihypertensive effects are different from those of beta-adrenergic blocking drugs like propranolol, which result in a decrease in heart rate and in cardiac output accompanied by little change or an increase in peripheral vascular resistance.[33,34] Propranolol but not verapamil attenuates the increases in systolic blood pressure during exercise; this is likely the result of blockade of exercise-induced activation of the sympathetic nervous system by propranolol, which does not occur with verapamil.

Beta-blocking drugs may exert their antihypertensive effects in part by decreasing plasma renin activity and

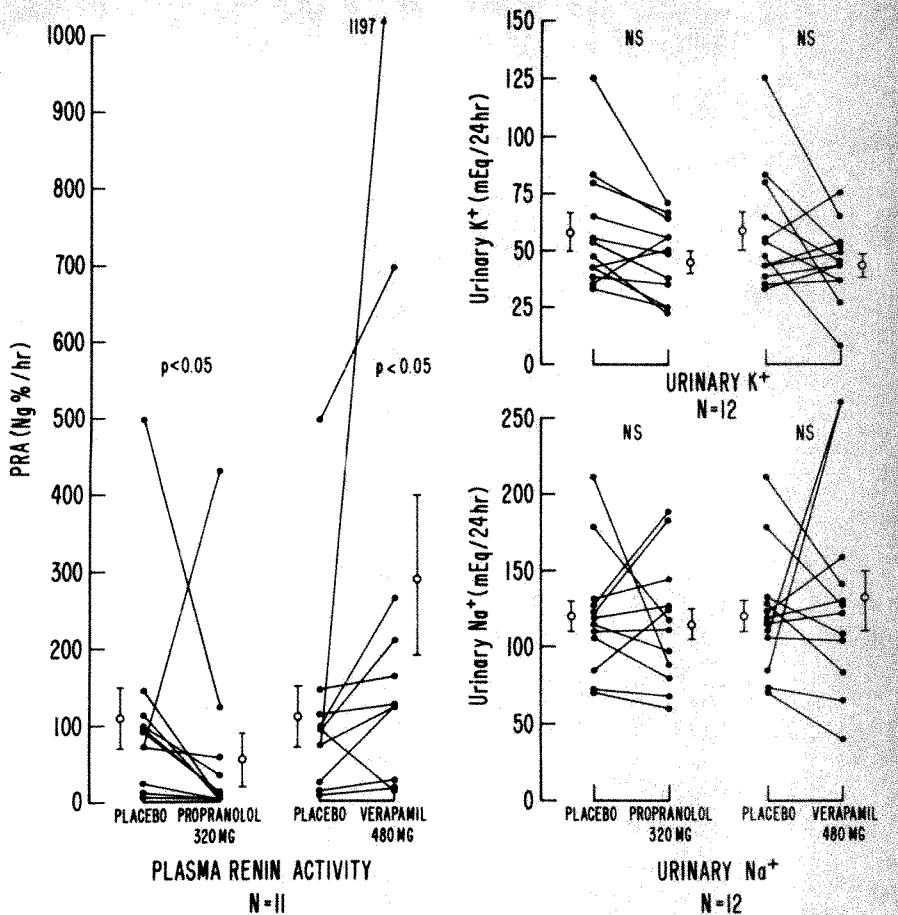

FIGURE 7. Effects of placebo, propranolol, and verapamil on 24 hour excretion of urinary electrolytes and plasma renin activity (PRA). The **closed circles** represent individual patient measurements; the **open circles** indicate mean values ± standard error of the mean.

plasma aldosterone.[35] In contrast, the hypotensive effects of vasodilator antihypertensive drugs are accompanied by an increase in plasma renin activity,[36,37] and our results indicate that verapamil (480 mg/day) does not differ from other vasodilator drugs in this regard; such increases are similar to those seen with large doses of nifedipine.[38] It is possible that the increases in plasma renin activity with 480 mg doses of verapamil serve to counteract the hypotensive effects of the drug, since the decreases in blood pressure were greater with 320 mg than with 480 mg of the drug; however, we did not measure changes in plasma renin activity with lower doses of verapamil. Despite the elevation in plasma renin activity with verapamil treatment, we observed no decrease in urinary sodium excretion and no gain in weight during either of the double-blind treatment periods.

Effects on angina and exercise tolerance: The effectiveness of verapamil in the management of patients with angina of effort and at rest has been shown in several placebo-controlled clinical trials.[3–8] Verapamil appears superior to propranolol in the treatment of patients with angina at rest[39] and is similar to propranolol in the management of patients with angina of effort.[4,40–42] In this study of 12 patients with both hypertension and angina pectoris, verapamil had a significantly greater effect on exercise tolerance than propranolol; however, the two drugs exerted similar effects on calculated exercise work, angina frequency, and nitroglycerin consumption. The maximal improvement in exercise tolerance and symptoms of angina were seen with higher doses of verapamil (480 mg daily) than those which achieved optimal control of blood pressure in these same patients.

At rest and at submaximal levels of exercise, both verapamil and propranolol produced a lower heart rate-blood pressure product than those seen during therapy with placebo. Hence, both drugs appear to exert their antianginal effects in part by reducing myocardial oxygen demands. However, for a given value of rate-pressure product, there was always more S-T segment depression with propranolol treatment than with verapamil therapy. Hence, verapamil appeared to exert antianginal effects in addition to its effects on myocardial oxygen consumption, possibly mediated by its direct effects on the coronary circulation.[43]

Relation between plasma drug levels and pharmacologic effects: Both verapamil and propranolol demonstrate first-pass hepatic metabolism when administered orally to patients with coronary artery disease.[27,44] This means that a substantial fraction of an oral dose will undergo hepatic biotransformation during the first pass through the liver and fail to reach the systemic circulation. Smaller doses may be completely metabolized with little residual drug reaching the systemic circulation, whereas larger doses can saturate the

hepatic enzyme systems and provide therapeutic blood levels. In this study, there was a linear relation between increments in the doses of both propranolol and verapamil and their respective plasma drug levels. Similar to findings with propranolol,[44] no relation was seen between verapamil plasma levels and its pharmacologic effects (on heart rate and blood pressure) in patients receiving the drug.

Clinical implications: In this study, verapamil was shown to be a safe and effective alternative to propranolol for reducing spontaneous attacks of angina pectoris, improving exercise tolerance, and reducing elevated blood pressure. Further double-blind studies investigating the long-term efficacy of verapamil and evaluating the use of verapamil in combination with other antihypertensive drugs (such as diuretics or beta-adrenergic blocking agents) need to be done. Verapamil provides a new conceptual approach to patients with both angina pectoris and systemic hypertension: calcium-entry blockade.

Acknowledgment

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Rationale for the Choice of Calcium Antagonists In Chronic Stable Angina

An Objective Double-Blind Placebo-Controlled Comparison of Nifedipine and Verapamil

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The effectiveness and safety of verapamil, nifedipine, and placebo in patients with chronic stable angina pectoris were evaluated and compared in two double-blind randomized crossover trials. In the first study, nifedipine (10 mg 3 times daily) was compared with placebo in 24 patients with chronic effort-related angina pectoris; no significant differences in exercise performance were observed with nifedipine compared with placebo. In the second study, the effects of verapamil (120 mg 3 times daily), nifedipine (20 mg 3 times daily), and placebo were compared in 32 patients with chronic stable angina using a double-blind crossover study design. Compared with placebo, both nifedipine and verapamil prolonged exercise duration (5.7 ± 0.3 minutes with placebo, 7.9 ± 0.5 minutes with nifedipine [p <0.001], and 10.0 ± 0.7 minutes with verapamil [p <0.001]), but the improvement with verapamil was greater than that seen with nifedipine (p <0.01). Seven patients had increasing angina with nifedipine, none did with verapamil; the exacerbation of angina during nifedipine therapy appeared related to our observation that, compared with placebo, patients receiving nifedipine had higher heart rates, while patients receiving verapamil had slower heart rates. This study indicates that, at the doses used, verapamil was more effective and better tolerated than nifedipine in patients with chronic stable angina pectoris.

The role of calcium antagonists in the management of patients with chronic stable angina of effort is well established,[1,2] but little work has been done to compare the effectiveness and safety of the two most widely employed agents, verapamil and nifedipine. Verapamil was first introduced as a coronary vasodilator[3] and was later demonstrated to be an effective antiarrhythmic agent.[4] The drug was initially suspected to be a beta-adrenergic blocking agent,[3] but later work showed that its effects were mediated by calcium-channel blockade[5]; it has been used in the treatment of supraventricular tachyarrhythmias,[6] angina pectoris,[7] and hypertrophic cardiomyopathy.[8] Nifedipine was developed as a specific calcium-channel blocker and has been advocated as an effective drug in variant and effort-related angina pectoris.[9,10]

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We conducted two randomized double-blind placebo-controlled crossover studies in patients with chronic stable angina pectoris. The first compared the effects of placebo and nifedipine (30 mg daily) in 24 patients; the second trial* compared the effects of verapamil (360 mg daily) with nifedipine (60 mg daily) and placebo in 32 patients. These studies show that, in the doses used in these studies, verapamil produces fewer adverse reactions and is superior to nifedipine in enhancing exercise performance in patients with effort-related angina pectoris.

Double-Blind Comparison of Placebo and Nifedipine

Patient Population

Twenty-four patients with chronic stable angina were entered into the first trial, after all previous antianginal medications had been withdrawn for at least 4 weeks. All patients had chest pain relieved by rest and by sublingual nitroglycerin and at least 1 mm horizontal S-T depression on standardized treadmill exercise testing. Patients with a recent myocardial infarction (within the last 4 months), with unstable or accelerating symptoms, with clinical congestive heart failure or

* This study was previously published.[11]

resting blood pressure over 160/100 mm Hg, or with insulin-dependent diabetes mellitus were excluded. No patient received digitalis, diuretics, or other cardiovascular agents before or during the study; the only medications permitted were the study drugs and sublingual nitroglycerin for anginal attacks.

Trial Design

This trial was a double-blind crossover study comparing placebo with nifedipine administered as 10 mg 3 times daily. Each drug was administered for 4 weeks with a 2 week crossover period between the study periods; only exercise testing was used for evaluation of the patients. All exercise tests were limited by angina, dyspnea, fatigue, or pain in the legs; all were performed in the morning 90 to 150 minutes after the last dose of the drugs and after 30 minutes of rest in a temperature-controlled laboratory. The details of the exercise testing procedure are reported elsewhere in this symposium.[12] Clinical efficacy and side effects were monitored closely. Statistical analysis was performed with a programmable calculator by the paired t test.

Results

Twenty-four patients entered this study, and 20 completed both placebo and active drug periods. The results are shown in Table I. There was no significant difference between placebo and nifedipine in a dose of 10 mg 3 times daily in any of the objective variables. Two patients were withdrawn due to uncontrolled angina while taking nifedipine.

TABLE I Comparative Effects of Placebo and Nifedipine, 30 mg Daily, in Patients With Chronic Stable Exertional Angina*

	Placebo	Nifedipine (10 mg tid)	p
Exercise time (min)	6.8 ± 0.6	6.9 ± 0.7	NS
1 mm time (min)	4.8 ± 0.7	4.6 ± 0.5	NS
ST↓ at peak effort (mm)	1.8 ± 0.2	1.7 ± 0.1	NS
Resting heart rate (beats/min)	74 ± 3	76 ± 3	NS
Maximal heart rate (beats/min)	129 ± 4	128 ± 4	NS

* Data are expressed as mean ± standard error of the mean. NS = not significant; ST↓ = S-T segment depression; tid = 3 times a day; 1 mm time refers to the duration of exercise until the appearance of 1 mm S-T segment depression.

Double-Blind Comparison of Nifedipine and Verapamil

Patient Population

Thirty-two patients with chronic stable angina entered the second trial. All patients had chest pain relieved by rest and by sublingual nitroglycerin and at least 1 mm horizontal S-T depression on standardized treadmill exercise testing. Patients with a recent myocardial infarction (within the last 4 months), with unstable or accelerating symptoms, with clinical congestive heart failure or resting blood pressure over 160/100 mm Hg, or with insulin-dependent diabetes mellitus were excluded. No patient received digitalis, diuretics, or other cardiovascular agents before or during the study; the only medications permitted were the study drugs and sublingual nitroglycerin for anginal attacks.

Trial Design

The second trial had 1 placebo and 2 active drug phases. After completion of an initial 2 week placebo run-in period, all patients entered a double-blind randomized crossover study consisting of 4 weeks of treatment with either nifedipine, 20 mg 3 times daily, or verapamil, 120 mg 3 times daily. At the end of 4 weeks, each patient received placebo for a 1 week washout period, after which the active drugs were crossed over, and each patient received 4 weeks of therapy with the alternate drug.

Exercise testing was repeated at the end of placebo, and after 4 weeks of each active drug therapy. All exercise tests were limited by angina, dyspnea, fatigue, or pain in the legs; all were performed in the morning 90 to 150 minutes after the last dose of the drugs and after 30 minutes of rest in a temperature-controlled laboratory. In addition, 24 hour ambulatory electrocardiographic monitoring with a frequency-modulated recorder was performed during each study period to establish changes in resting heart rate, directional changes in S-T segments, and the appearance of conduction defects. The details of the exercise testing and electrocardiographic monitoring procedures are reported elsewhere in this symposium.[12]

Statistical analyses were performed with a programmable calculator by t test for paired data.

Results

Of the 32 patients who entered the trial, 1 was withdrawn during placebo therapy due to detection of hypochromic anemia. Three patients were withdrawn within 3 days of the first leg of the crossover while receiving nifedipine. The remaining 28 patients completed 4 weeks of treatment with the first randomized drug (nifedipine in 13 and verapamil in 15). Two weeks after the crossover to nifedipine had been completed, 4 more patients (who had successfully completed the verapamil phase of the study) were withdrawn due to side effects; however, they completed all the evaluations while on treatment with nifedipine for 2 weeks. The data consist of variables from the 28 patients who completed all the tests.

Exercise duration (Fig. 1, Tables II and III: The duration of exercise during placebo therapy (5.7 ± 0.3 minutes) was prolonged by both nifedipine (7.9 ± 0.5 minutes, $p < 0.001$) and verapamil (10.0 ± 0.7 minutes, $p < 0.001$), but the improvement with verapamil was

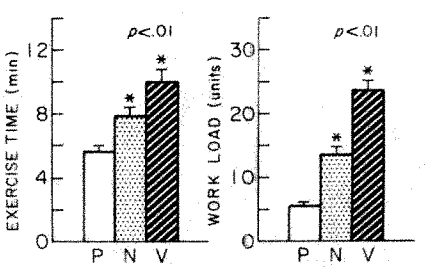

FIGURE 1. Duration of exercise (**left panel**) and workload (**right panel**) during therapy with placebo (P), nifedipine (N), and verapamil (V). Data are shown as means ± standard error of the mean. **Asterisks** indicate significance of differences between active drug therapy and placebo. P values indicate significance of differences between nifedipine and verapamil.

significantly greater than that with nifedipine ($p < 0.01$). All 28 patients stopped exertion during treadmill testing because of angina during the placebo phase, 20 stopped because of angina while taking nifedipine, and 17 patients had their exercise tests limited by angina while receiving verapamil. The exercise time with verapamil was longer than with nifedipine in 22 patients, shorter in 5 patients, and similar in 1 patient. The maximal workload achieved averaged 5.6 ± 0.4 units with placebo, 13.6 ± 0.9 units with nifedipine ($p < 0.001$ versus placebo), and 23.8 ± 1.2 units with verapamil ($p < 0.001$ versus placebo and $p < 0.001$ versus nifedipine).

Exercise variables and electrocardiographic S-T segment responses (Fig. 2, Table II): The time to 1 mm S-T segment depression during placebo therapy (3.9 ± 0.3 minutes) was prolonged by both verapamil and propranolol, but the improvement with verapamil (7.1 ± 0.5 minutes) was significantly greater than that with nifedipine (5.8 ± 0.4 minutes) ($p < 0.01$); this was true as well for the time to 2 mm S-T depression. At the same workload achieved during placebo therapy, both nifedipine and verapamil reduced the magnitude of S-T depression, but the improvement seen with verapamil was greater ($p < 0.05$). However, the magnitude of S-T

TABLE II Comparative Effects of Placebo, Nifedipine, and Verapamil in Patients With Chronic Stable Exertional Angina*

	Placebo	Nifedipine (60 mg daily)	Verapamil (360 mg daily)	p: Placebo vs Nifedipine	p: Placebo vs Verapamil	p: Nifedipine vs Verapamil
Exercise time (min)	5.7 ± 0.3	7.9 ± 0.5	10.0 ± 0.7	<0.001	<0.001	<0.001
Workload (units)	5.6 ± 0.4	13.6 ± 0.9	23.8 ± 1.2	<0.001	<0.001	<0.001
Resting heart rate (beats/min)	74 ± 2	77 ± 2	68 ± 2	NS	<0.01	<0.001
Maximal heart rate (beats/min)	125 ± 3	130 ± 3	124 ± 3	<0.05	NS	<0.01
Double product at peak effort (beats × mm Hg/min)	154 ± 8	159 ± 8	164 ± 6	NS	NS	NS
1 mm time (min)	3.9 ± 0.3	5.8 ± 0.4	7.1 ± 0.5	<0.001	<0.001	<0.01
2 mm time (min)	5.3 ± 0.4	7.5 ± 0.4	9.5 ± 0.7	<0.001	<0.001	<0.001
$ST_{\downarrow}$ at peak effort (mm)	2.0 ± 0.2	2.0 ± 0.2	1.8 ± 0.2	NS	NS	NS
$ST_{\downarrow}$ at same workload as placebo (mm)	1.8 ± 0.2	1.0 ± 0.2	0.7 ± 0.2	<0.001	<0.001	<0.05
Heart rate same workload as placebo (beats/min)	122 ± 3	117 ± 3	106 ± 3	<0.05	<0.001	<0.001

* Data are expressed as means ± standard error of the mean. NS = not significant; $ST_{\downarrow}$ = S-T segment depression.

TABLE III Demographic Data and Clinical Results With Placebo (P), Verapamil (V), and Nifedipine (N)

Case	Age (yr) & Sex	Exercise Time (min) P	V	N	Preference	Adverse Effects
1	69F	5.1	9.3	8.1	V	...
2	50M	9.9	18.5	10.9	V	Angina on N
3	56M	4.9	15.3	12.3	Equal	...
4	56M	6.6	11.0	11.2	Equal	...
5	65M	4.3	8.1	5.8	V	...
6	64M	9.8	13.9	11.0	V	...
7	69M	5.6	11.4	8.8	V	...
8	51M	6.7	11.6	9.4	V	Angina on N
9	66M	5.1	12.8	10.1	V	...
10	67M	5.6	8.5	5.3	Equal	...
11	58M		(Withdrawn)		...	Hypochromic anemia on P
12	39M	5.0	5.8	5.4	Equal	...
13	60M	4.4	11.2	7.7	V	Angina on N
14	54M	4.6	9.2	7.0	V	...
15	66M	3.3	9.2	5.5	Equal	...
16	53M	4.7	12.1	5.5	V	...
17	55M	7.2	8.9	8.2	Equal	...
18	55M		(Withdrawn)		...	Severe muscle weakness on N
19	68M	3.3	3.8	3.0	Equal	Angina on N
20	49M	5.2	8.5	6.3	V	...
21	53M	4.9	11.9	7.1	V	...
22	60M	4.6	11.5	7.1	V	...
23	66M	3.9	5.6	7.0	N	...
24	53M		((Withdrawn)		...	Accelerated angina on N
25	61M	5.4	14.1	12.0	Equal	...
26	54M	7.6	12.4	12.5	Equal	...
27	59M	5.0	6.4	6.4	N	...
28	59M	4.8	7.9	9.4	N	...
29	50M	8.4	7.8	7.0	N	...
30	66F		(Withdrawn)		...	Palpitations, edema, angina on N
31	60M	5.9	8.0	9.0	V	...
32	65M	5.2	13.1	8.1	V	...

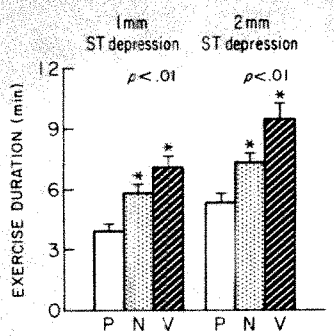

FIGURE 2. Time on a treadmill exercise test to the development of 1 and 2 mm S-T depression during treatment with placebo (P), nifedipine (N), and verapamil (V). Data are shown as means ± standard error of the mean. **Asterisks** indicate significance of differences between active drug therapy and placebo. P values indicate significance of differences between nifedipine and verapamil.

depression at maximal exercise was unchanged by both drugs; this S-T depression, however, was seen after a longer duration of exercise with both nifedipine and verapamil. Neither drug significantly altered the double-product at peak effort.

Compared with placebo (74 ± 2 beats/min), heart rate decreased with verapamil (68 ± 2 beats/min, p <0.001), but did not change with nifedipine (77 ± 2 beats/min). The heart rate at the same workload achieved at peak effort during placebo therapy was reduced by both drugs, but the effects of verapamil were more pronounced (p <0.001). Nifedipine *increased* the heart rate observed at peak effort (p <0.001); this was not altered by verapamil.

Twenty-four hour ambulatory monitoring (Fig. 3 and 4): The pooled mean hourly heart rate on placebo, verapamil, and propranolol was related to clock time and expressed as a continuous curve. Verapamil reduced heart rate throughout the day, but heart rate was increased with nifedipine (Fig. 3). The mean number of minutes during which the heart rate exceeded 100 beats/min was 101 ± 10 minutes with nifedipine, which was significantly higher than that with placebo (42 ± 5 minutes); both were higher (p <0.001) than that during therapy with verapamil (4 ± 1 minutes). The number of episodes (in 24 hours) of S-T depression greater than 1 mm was 15 ± 2 on placebo; this remained unchanged with nifedipine but was markedly reduced by verapamil (9 ± 2, p <0.001) (Fig. 4).

Adverse reactions (Table III): During verapamil therapy, no patient exhibited evidence of congestive heart failure or atrioventricular conduction disturbance. After 2 weeks on verapamil, one patient developed mild pedal edema which responded to therapy with diuretics. Minor side effects included constipation in 6 patients, headache in 2, and giddiness in 1. None required withdrawal of treatment.

In contrast, major adverse effects were observed during treatment with nifedipine. Three patients had to be withdrawn from the trial during the nifedipine phase before completing 2 weeks of treatment: one patient had unstable angina, which required intraaortic balloon pumping for relief; another patient had severe muscular weakness and tremor, which disappeared within 24 hours after withdrawal of nifedipine; and the third patient had ankle edema, palpitations, angina, and severe headache. Four other patients were withdrawn from nifedipine after completing 2 weeks of therapy because of palpitations, headaches, and angina provoked by nifedipine ingestion. The Holter monitoring record in one of these patients is shown in Figure 5. This patient had a rapid increase in heart rate which began 45 minutes after ingestion of the drug and persisted for about 1 hour; this was accompanied by S-T segment depression and angina. Minor side effects during treatment with nifedipine, which did not necessitate withdrawal, including flushing, tremors, mild pedal edema, and palpitations.

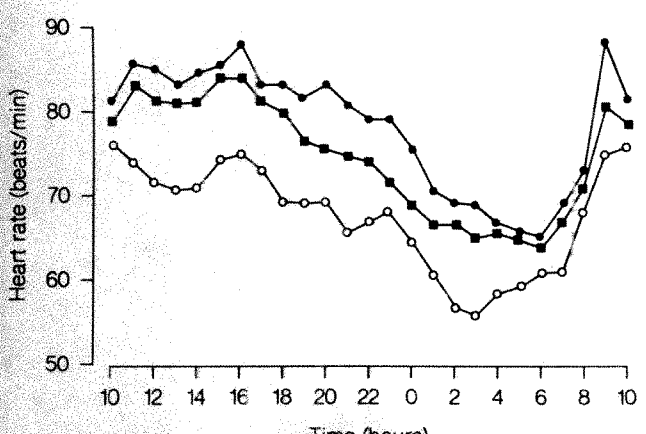

FIGURE 3. Pooled hourly mean heart rates of 28 patients taking placebo (**solid squares**), verapamil (**open circles**), and nifedipine (**solid circles**). Note the higher hourly mean heart rates with nifedipine and the lower heart rate during therapy with verapamil.

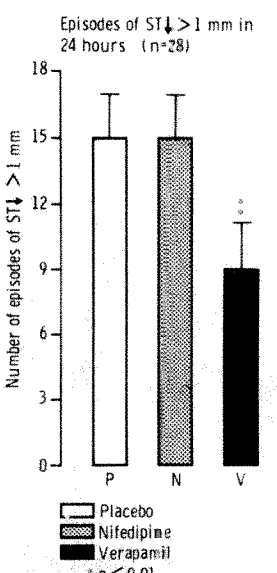

FIGURE 4. The mean number of episodes of S-T depression (ST↓) in 24 hour treatment with placebo (P), verapamil (V), and nifedipine (N). Only verapamil produced a significant reduction in the number of episodes.

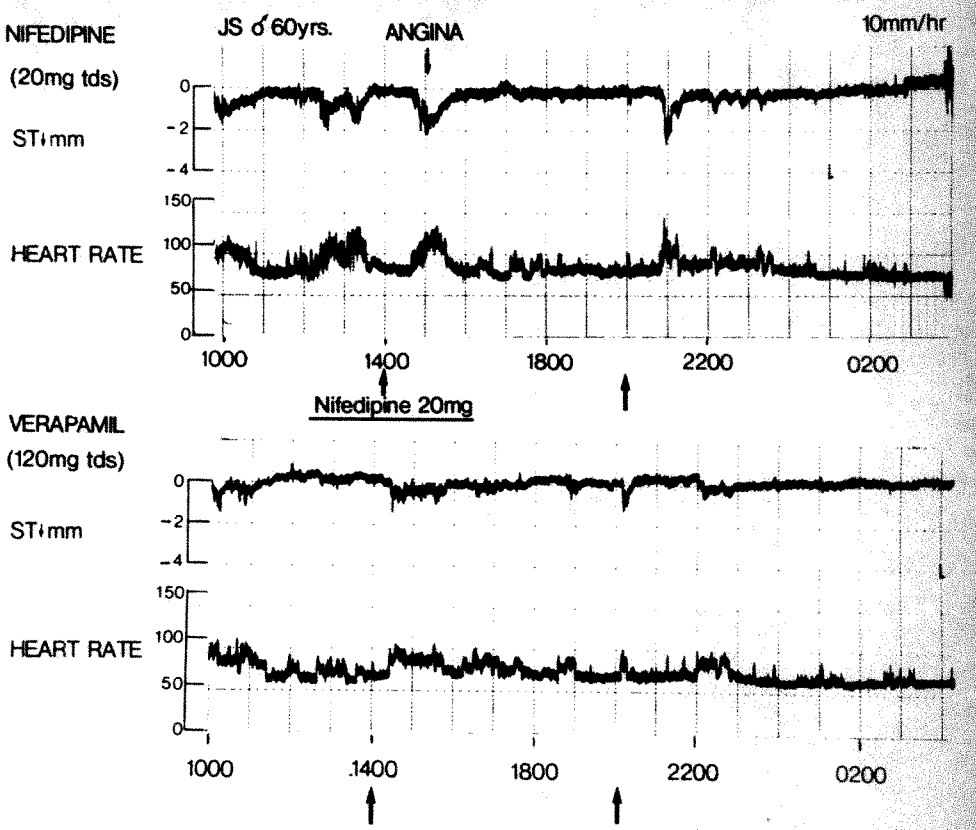

FIGURE 5. Twenty-four hour ambulatory heart rate and S-T segment trend of a patient who had angina after nifedipine and withdrew from the trial after 2 weeks of the nifedipine phase. The **top channel** of both trends shows calibrated S-T segment levels and the **bottom channel** shows the heart rate. Clock time is shown on the **horizontal axis**. The times of verapamil and nifedipine ingestion are marked by the **upright arrows** at 1400 and 2000 hours. Note the increase in heart rate within 45 minutes of nifedipine administration, accompanied by marked S-T segment depression and angina; similar episodes of S-T segment depression and angina were not seen after the administration of verapamil. The heart rate was consistently higher with nifedipine than during therapy with verapamil.

Discussion

Verapamil Versus Nifedipine in Chronic Stable Angina

Although several controlled clinical trials have established the effectiveness of verapamil and nifedipine in the management of patients with stable and unstable angina pectoris,[9–13] few trials have compared the effectiveness of the two drugs. Dawson et al.[14] recently compared nifedipine and verapamil in 16 patients with effort-related angina who entered a double-blind randomized trial using the same doses as those employed in the present report. Both drugs produced a similar decrease in the frequency of anginal attacks and the number of nitroglycerin tablets consumed, and a similar increase in exercise duration; however, side effects were significantly more common with nifedipine. Thus, these investigators concluded that verapamil appeared to be the calcium antagonist agent of choice in patients with chronic stable angina pectoris.[14] The ablity of this trial to detect significant differences in *effectiveness* between verapamil and nifedipine was limited by the small number of patients evaluated and by the lack of ambulatory electrocardiographic monitoring to detect asymptomatic episodes of ischemia.

The present study is the first placebo-controlled randomized clinical trial evaluating these two agents in patients with exertional angina using exercise testing *and* Holter monitoring. Compared with placebo, both verapamil and nifedipine increased exercise tolerance and the quantity of work performed during symptom-limited exercise, while decreasing the magnitude of S-T segment depression for a given workload. However, in the doses administered, the magnitude of improvement with verapamil (360 mg daily) was superior to that seen with nifedipine (60 mg daily) for all variables measured. Verapamil significantly reduced the number of asymptomatic episodes of ischemia, as determined by S-T segment shifts on Holter monitoring, whereas nifedipine did not. Moreover, therapy with verapamil was better tolerated than was treatment with nifedipine. Few adverse reactions were noted with verapamil; none were serious, and none required discontinuation of the drug. In contrast, 7 of the 32 patients developed side effects during nifedipine therapy serious enough to require its withdrawal; 6 of the 7 patients had worsening angina. These results are very similar to the findings of Dawson et al.[14]; the differences we observed in effectiveness between the two drugs was likely related to the larger number of patients in our trial.

Validation of the Study Design

When designing the present trial, we made every effort to ensure objectivity of data collection and interpretation. The trial was randomized, double-blind, and placebo-controlled, and used two sets of objective end points. Exercise testing was used for quantification of exercise tolerance under highly observed and controlled conditions, and ambulatory electrocardiographic monitoring was used to assess uncontrolled environmental influences as well as ischemic responses at rest. All of the data were analyzed by computer without knowledge of the drug assignment, and none of it relied

on subjective interpretation by either patients or by physicians.

Our protocol, like that of Dawson et al.,[14] compared fixed doses of verapamil and nifedipine rather than individually titrated doses of both drugs. The dose of verapamil used (360 mg daily) was chosen because we and others have found this dose to be well-tolerated and highly effective in relieving anginal symptoms for long periods.[7,15–17] Although both higher and lower doses of verapamil have been used by other investigators, lower doses (240 mg daily) have not been consistently effective,[18] and higher doses (480 mg daily) have been reported to produce greater adverse effects without producing significant additional benefits.[17] The dose of nifedipine used (60 mg daily) was chosen because our earlier study using 30 mg daily did not show significant effects at this dose compared with placebo. Furthermore, 60 mg daily was the principal dose employed in the multicenter placebo-controlled trials of nifedipine in effort-related angina pectoris recently conducted in the United States.[10] Although we and others have found 60 mg daily more effective than 30 mg daily, the higher dose also produced greater adverse effects. Although a still higher dose of nifedipine (30 mg or more per dose, 90 to 120 mg daily) might have improved exercise tolerance more than in the present trial, it is likely that such a dose would also have produced a still greater incidence of adverse reactions than we observed.

Previous Comparative Trials of Verapamil and Nifedipine

Winniford et al.[19] compared the effectiveness of safety of verapamil and nifedipine in patients with variant angina, most of whom had nonobstructive coronary artery disease. Their patients received verapamil (mean dose 450 mg daily) in a double-blind fashion but received open-label therapy with nifedipine (mean dose 71 mg daily). Given the limitations of this type of comparison, the two drugs were equally effective in abolishing symptomatic and asymptomatic episodes of ischemia. However, adverse effects were more common with nifedipine than with verapamil. None of the 27 patients in this study required a reduction in dose or discontinuation of therapy while taking verapamil, whereas 3 patients discontinued therapy and 7 patients had dose-limiting adverse effects while taking nifedipine.

Mechanisms Underlying Differences Between Verapamil and Nifedipine

In contrast to the comparable efficacy of the two drugs in patients with variant angina, we found verapamil superior to and better tolerated than nifedipine in patients with effort-related symptoms. The differences in the findings of the two studies are explicable if one recalls that the mechanisms underlying the antianginal effects of the calcium antagonists in exercise-provoked ischemia differ from those in variant angina. The benefits observed in patients with effort-related symptoms are likely mediated by the drugs' systemic vasodilator actions rather than their ability to block coronary vasospasm.[20,21] By reducing peripheral resistance, both verapamil and nifedipine decrease myocardial oxygen requirements for a given workload. Unfortunately, any drug-induced peripheral vasodilation causes sympathetically mediated reflex tachycardia which, if left unopposed, may detract from a drug's antianginal effects and provoke adverse reactions (such as palpitations, headaches, and angina) characteristic of sympathetic hyperactivity.[1,22] This reflex sympathetic activation is not affected by nifedipine but is attenuated by verapamil, both directly by its inhibitory action on the sinoatrial node and indirectly by a nonspecific antagonist effect on the adrenergic nervous system.[1,5] We would therefore expect verapamil to be more effective and better tolerated than nifedipine in patients with effort-related symptoms.

Our observations are consistent with these concepts. Whereas verapamil produced a mild slowing of the heart rate and nearly abolished the number of episodes of heart rate over 100 beats/min, nifedipine produced a mild reflex tachycardia, such that heart rates over 100 beats/min were seen significantly more often with nifedipine than with placebo. In 4 patients in the present study, this reflex tachycardia was sufficiently severe to provoke episodes of angina at rest, shortly after ingestion of a dose of nifedipine. Similar occurrences have been reported by others.[23–28] Therefore, the less marked effects of nifedipine in controlling angina may be related to the deleterious effects of drug-induced tachycardia, which may offset the otherwise beneficial effects of vasodilation. Successful and safe antianginal therapy with nifedipine, therefore, appears to require effective attenuation of drug-induced increases in heart rate by concomitant therapy with a beta-adrenergic blocking drug; supplemental beta blockade is not needed with verapamil. However, concomitant therapy with nifedipine and beta blocking agents may result in excessive hypotension and in the exacerbation of congestive heart failure[24,29–31]; hence, such therapy should be used with caution.

In conclusion, verapamil appears to be a more effective and better tolerated drug than nifedipine in the management of patients with chronic stable effort-related angina pectoris. The differences in the clinical responses seen with the 2 drugs appear to be explicable by differences in their effects on heart rate.

Acknowledgment

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Clinical Relevance of Verapamil Plasma Levels in Stable Angina Pectoris

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Plasma levels of verapamil and norverapamil were evaluated in 77 patients who received oral verapamil for treatment of angina pectoris. There was a sixfold interpatient variation in verapamil plasma concentrations, but plasma concentrations were linearly related to doses of the drug (240 to 480 mg/day) in the same patient ($r = 0.81$). Plasma concentrations of norverapamil, the major active metabolite of verapamil, were similar to those of verapamil.

Although verapamil produced a significant improvement in exercise tolerance in most patients, the increase in exercise time was not related to plasma levels of the drug; however, most patients with improvement had plasma levels exceeding 100 ng/ml. An increase in the dose of verapamil from 320 to 480 mg daily produced a substantial (71%) increase in plasma levels of the drug but no significant increase in exercise tolerance (4%).

The average increase in the P-R interval with 480 mg of verapamil in these 77 patients was small (8%) (161 ± 18 to 174 ± 22 ms); only six patients had first-degree heart block. These minor effects on atrioventricular conduction were noted despite plasma verapamil concentrations in 76 patients that exceeded 100 ng/ml, a level that successfully converts supraventricular tachycardias after intravenous drug administration. The differences between the effects of oral and intravenous verapamil on atrioventricular conduction may be the result of stereoselective hepatic inactivation of verapamil's *l*-isomer.

Determination of plasma levels of verapamil is of limited value in the management of patients with angina pectoris, but may be useful in the identification of nonresponders with plasma levels less than 100 ng/ml who may benefit from a further increment in drug dose.

The direct application of pharmacokinetic principles to the optimization of individual dosing regimens has become an important aspect of pharmacotherapy. Verapamil is a calcium channel-blocking agent which is effective in the treatment of angina,[1] atrial arrhythmias,[2] systemic hypertension,[3] and hypertrophic cardiomyopathy.[4] Although there have been several reports on the pharmacokinetics of verapamil in both normal subjects and patients after administration of a single dose,[5-7] few studies have attempted to define therapeutic plasma levels during long-term oral administration of the drug in patients with ischemic heart disease.

Long-term therapy with verapamil is associated with an extremely wide interpatient variation in peak plasma levels. Because the gastrointestinal absorption of verapamil is rapid and complete,[5] this variation is likely due to the high first-pass hepatic metabolism of the drug.[5,6] Twelve metabolites of verapamil have been identified, most in only small amounts.[8] The only metabolite that appears to possess significant pharmacologic activity is norverapamil, which has about 20% of

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the activity of the parent compound[9] and is not formed after intravenous administration of verapamil.[7] The objective of this investigation was to evaluate the interindividual differences in verapamil and norverapamil plasma levels during long-term therapy with verapamil and define a relation between plasma concentration of the drug and its antianginal effect.

Methods

Study patients: All patients were enrolled in one of several well-controlled multicenter clinical trials, sponsored by the Knoll Pharmaceutical Company, in which verapamil was compared with either placebo or propranolol.[10–13] All patients for whom plasma samples were available for analysis form the basis of the present report. No patient was excluded because of failure to respond to verapamil therapy or because of the development of adverse effects.

The patient group consisted of 77 patients (74 men and 3 women). All patients had effort-related angina pectoris with 3 to 15 anginal episodes per week and S-T segment changes of 1.0 mm or greater on treadmill exercise testing before treatment. The average (± standard deviation [SD]) number of episodes of angina at rest per week was 1.2 ± 0.6 and the average number of episodes of exertional angina per week was 7.3 ± 1.3, as recorded by each patient in a diary. The age of the patients averaged 58 ± 8 years (SD).

All cardioactive medications except sublingual nitroglycerin tablets were discontinued for 48 hours before entry into the study. Each study included a 2 week placebo-controlled period followed by a dose-titration phase, during which each patient received verapamil at doses of 240 mg/day (80 mg 3 times daily), 320 mg/day (80 mg 4 times daily), and 480 mg/day (120 mg 4 times daily or 160 mg 3 times daily) for periods of 1 week each. Exercise tolerance was measured for each patient by means of a standardized symptom-limited exercise test (using the Bruce protocol) at the end of the placebo period as well as at the end of 1 or more of the 3 verapamil treatment periods. In one study of 20 patients,[11] peak plasma verapamil concentrations were measured while patients were receiving 240 mg/day, 320 mg/day, and 480 mg/day, and exercise tolerance was measured at the 2 largest doses of verapamil.

Plasma verapamil determinations: Blood samples for plasma levels of verapamil and its N-demethylated metabolite (norverapamil) were drawn 1.5 to 2.5 hours after the last dose of verapamil; previous studies indicated that peak levels of both compounds occurred at this time.[7] Plasma levels of verapamil and norverapamil were quantitated by high pressure liquid chromatography at Bio-Science Laboratories, Bellwood, Illinois.[14] The assay utilized has been shown to be linear for plasma verapamil concentrations between 10 and 1,000 ng/ml.

Statistical analysis: Data are expressed as mean values ± SD. Differences from baseline were analyzed using analysis of variance procedures. Regression analysis was employed using a linear least squares fit of the data points.

Results

Interpatient variation in plasma levels: There was little relation between the dose of verapamil and plasma levels of the drug in the 77 patients in the present study; with 480 mg daily of verapamil, plasma drug levels showed a sixfold interpatient variation (Fig. 1). Four centers[10–12] administered verapamil at a dose of 120 mg every 6 hours, whereas one center[13] employed a dose of 160 mg every 8 hours. The average peak verapamil plasma level in the 56 patients who received the drug as 120 mg every 6 hours (301 ± 53 ng/ml) was similar to that in the 21 patients who were given 160 mg every 8 hours (361 ± 166 ng/ml). Five of the 77 patients had

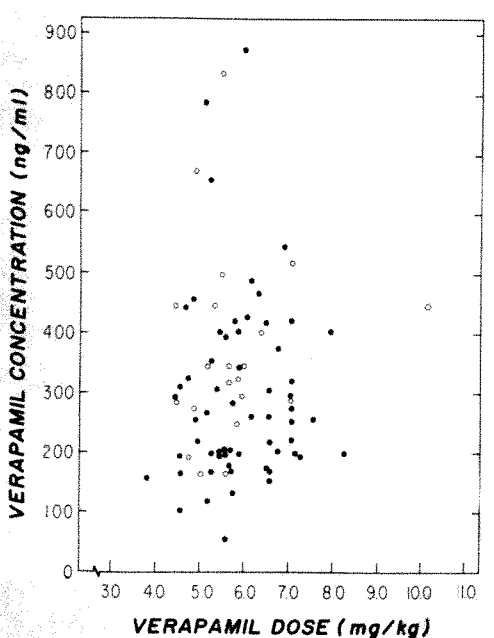

FIGURE 1. Peak verapamil concentrations versus dose in 77 patients. All patients received 480 mg of oral verapamil daily, as either 120 mg verapamil every 6 hours (**closed circles**) or 160 mg verapamil every 8 hours (**open circles**).

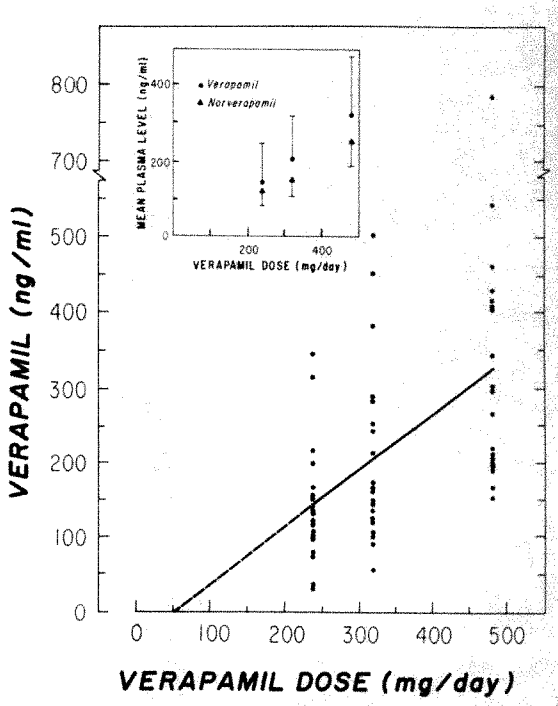

FIGURE 2. Peak verapamil concentrations after daily doses of 240, 320, and 480 mg verapamil in 20 patients. A highly significant linear relation ($r = 0.81$) was found between drug level and dose in the same patient. The **inset** depicts the mean (±SD) plasma levels of verapamil and norverapamil in these patients.

plasma verapamil levels greater than 600 ng/ml, but none exhibited adverse effects with the drug despite these very high levels.

Intrapatient variation in plasma levels: In contrast to the wide intrapatient variation, there was a close relation in the *same* patients between verapamil dose and the observed plasma levels of the drug. In a subgroup of 20 patients studied at 3 different dose levels, mean plasma concentrations of verapamil were linearly related to the dose of the drug for doses of 240 to 480 mg/day ($r = 0.81$). Mean plasma drug levels from these 20 patients were extrapolated to zero drug concentration at a dose of about 50 mg/day (Fig. 2).

Plasma levels of verapamil versus norverapamil: Plasma levels of verapamil were linearly related ($r = 0.86$) to those of its major metabolite, norverapamil, in all 77 patients who received long-term therapy with doses of oral verapamil ranging from 240 to 480 mg daily (Fig. 3). In the 20 patients who received three dose levels of the drug, steady-state plasma levels of norverapamil were approximately equal to those of the parent compound (Fig. 2 inset); the average plasma concentrations after the 240, 320, and 480 mg/day doses were 141, 206, and 323 ng/ml of verapamil and 128, 177, and 255 ng/ml of norverapamil, respectively.

Relation between plasma verapamil levels and therapeutic effects (Fig. 4): Eighteen of the 20 patients who received two different dose levels of the drug (320 mg and 480 mg daily) had complete sets of data points. Verapamil in a dose of 320 mg daily produced an overall increase in exercise duration (304 ± 85 seconds on placebo to 438 ± 108 seconds, $p < 0.05$). A greater than 20% improvement was observed in 14 of the 18 patients; all but 2 of these 14 patients had plasma verapamil levels greater than 100 ng/ml. There was no relation between the magnitude of improvement and plasma levels of the drug.

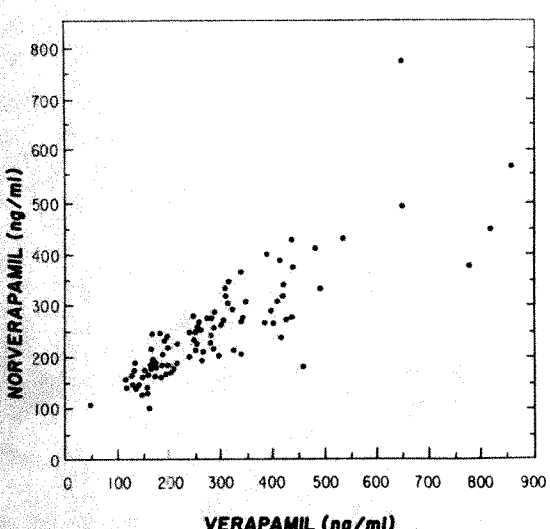

FIGURE 3. Correlation between plasma concentrations of verapamil and norverapamil in patients receiving verapamil in daily doses of 240, 320, and 480 mg.

When the dose of verapamil was increased in these 18 patients from 320 to 480 mg daily, exercise tolerance failed to improve significantly (from 438 ± 108 to 450 ± 132 seconds). Although 15 patients had a further increase in exercise tolerance, this averaged only 4% (that is, 16 seconds) despite a 71% (135 ng/ml) increase in plasma verapamil concentrations; exercise time deteriorated in 3 patients despite an increase in drug dose and a corresponding increase in circulating drug levels.

Although P-R interval prolongation was frequently seen after administration of verapamil in the 77 patients who received 480 mg daily of the drug, the average increase was only 8% (161 ± 18 to 174 ± 22 ms), although plasma verapamil concentrations exceeded 100 ng/ml in 76 patients; only six patients had first-degree heart block (P-R interval over 200 ms).

Discussion

Pharmacokinetics of verapamil: The recent development of sensitive and specific assay methods[14] has permitted delineation of the kinetic profile and metabolism of verapamil. The gastrointestinal absorption of verapamil is rapid and complete (92 to 100%)[5,7]; however, only 22% of the drug reaches the systemic circulation, largely because of its rapid metabolism in the liver during its first pass through the portal circulation.[5,7,8] Approximately 90% of verapamil is bound to plasma proteins[5]; however, this binding is not concentration-dependent over the range of 10 to 2,000 ng/ml. Verapamil protein binding is not significantly altered by renal insufficiency or cardiac catheterization, or by the addition of warfarin.[15]

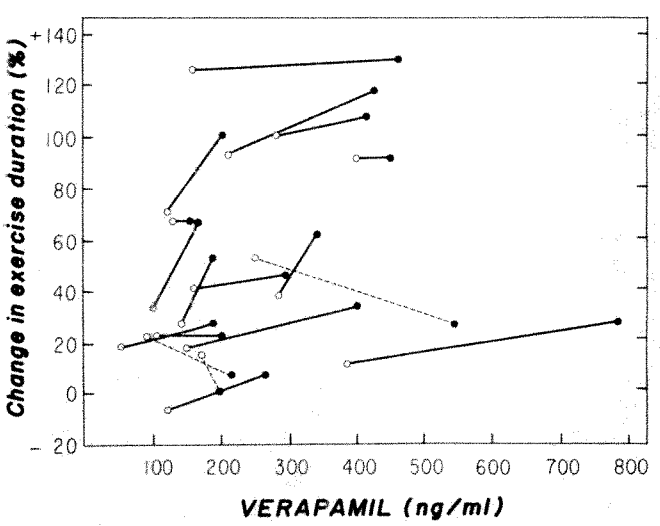

FIGURE 4. Relation between steady-state plasma levels of verapamil and its pharmacologic effects as assessed by maximal exercise tolerance testing. The percent change in exercise duration from baseline (placebo) is related to the peak verapamil plasma level measured immediately before exercise testing. Patients were tested at verapamil doses of 320 mg/day (**open circles**) or 480 mg/day (**closed circles**). Results are shown for 18 patients in whom complete data were available. Three patients (**dashed lines**) showed a decrease in exercise tolerance with increases in the dose of verapamil.

The elimination half-life is about 5 hours for verapamil and about 8 to 10 hours for norverapamil.[5,16] In a fashion similar to that for propranolol,[17] the half-life of verapamil increases with repeated oral administration of the drug because of the saturation of hepatic enzyme systems as plasma levels increase[6,16,18]; that is verapamil hepatic clearance decreases with increasing plasma drug concentrations. After 6 to 10 consecutive doses, the half-life increases to a range of 6 to 12 hours[18] without a further increase during continued administration for one year or longer.[6] In patients with liver dysfunction, the half-life of verapamil is prolonged up to 14 to 16 hours, and plasma levels of verapamil during long-term oral administration are five times those seen in patients with normal hepatic function.[19] Accordingly, the dose of verapamil should be reduced by one third to one fifth in patients with impaired hepatic function.[19,20]

Verapamil dose and plasma levels: We found that peak plasma verapamil concentrations at steady-state were linearly related to the dose of verapamil administered when drug dosage was increased in the same patients. Doubling the dose of verapamil resulted in a corresponding twofold increase in mean plasma concentrations of both verapamil and norverapamil. This linear accumulation of plasma verapamil during the administration of 240 to 480 mg/day of the drug indicates that hepatic metabolism of the drug is not characterized by a threshold response.

Plasma verapamil levels and therapeutic response: Plasma concentrations of verapamil and norverapamil varied about sixfold after 1 week's treatment with 480 mg daily, averaging 301 ng/ml in patients receiving 120 mg every 6 hours and 361 ng/ml in patients receiving 160 mg every 8 hours. These results are similar to those of Woodcock et al.,[21] who reported mean steady-state verapamil levels of 355 ng/ml with a 13-fold variation in plasma levels in patients with hypertrophic obstructive cardiomyopathy receiving 160 mg every 8 hours. The wide variation in plasma verapamil levels is likely the result of the high and variable degree of hepatic metabolic inactivation of orally administered drug. Similar interpatient variations in peak levels have been reported for the beta-adrenergic blocking agents propranolol[17] and metoprolol.[22]

Most patients who had improvement during long-term verapamil therapy had plasma levels of the drug greater than 100 ng/ml; this is similar to the plasma drug levels required for successful conversion of supraventricular tachycardia to sinus rhythm.[23] However, plasma verapamil concentrations correlated poorly with the *magnitude* of improvement in exercise duration in our patients with effort-related angina pectoris; it was not possible to predict a patient's improvement in exercise tolerance based on plasma drug levels. Anginal symptoms improved in most patients with a dose of 320 mg of verapamil daily; although some patients showed further improvement with increments in dose to 480 mg daily, such benefits were small and inconsistent, despite substantial further increases in plasma verapamil concentrations. Hence, daily doses of 320 mg of verapamil may provide near-maximal therapeutic benefit in patients with effort-related angina pectoris; other investigators have similarly suggested that the optimal dose of verapamil for angina therapy is 320 mg daily (80 mg every 6 hours)[13] or 360 mg daily (120 mg every 8 hours).[24] As with any antianginal drug, upward titration of dosage may be necessary in selected patients in order to obtain maximal benefits with verapamil.

The only drug effect reported to be significantly related to the plasma levels of verapamil is the prolongation of the electrocardiographic P-R interval; this relation has been established for both intravenous and oral drug administration.[7,25] However, in the present study, verapamil (480 mg daily) produced an increase in the P-R interval of only 13 ms (8%), even though 76 of the 77 patients achieved plasma drug levels exceeding 100 ng/ml, a level that produces effects on atrioventricular conduction sufficient to terminate most supraventricular tachycardias.[23] This rather small increase in the P-R interval during long-term oral administration might be explained by the hypothesis of Eichelbaum et al.[25] They observed that patients required plasma levels of verapamil 2 to 3 times greater during oral therapy than after intravenous drug administration in order to achieve similar effects on the P-R interval. Because the *l*-isomer of verapamil is 8 to 10 times more active than the *d*-isomer in prolonging atrioventricular conduction,[26] these investigators hypothesized that the *l*-isomer might be selectively metabolized by the liver, and hence plasma levels of the drug during oral administration might consist primarily of the less depressant *d*-isomer; in contrast, after intravenous drug administration, *d*- and *l*-isomers are present in equal concentrations. This could explain the smaller increases in the P-R interval during oral administration of verapamil than during intravenous therapy. Stereoselective hepatic inactivation has been shown to occur during long-term oral therapy with propranolol.[27]

Peak verapamil levels up to 900 ng/ml were observed in some of our patients without adverse effects; hence, delineation of a toxic level of verapamil is not possible from the data available in the present study. Toxic cardiovascular reactions (bradycardia, atrioventricular block, and hypotension) have been reported after massive doses of verapamil (2.0 to 5.6 g),[28,29] usually in setting of attempted self-poisoning in persons with normal ventricular function; recovery has usually occurred within 24 to 36 hours using only supportive measures. Plasma verapamil levels of 4,000 ng/ml were measured after the ingestion of 3.2 g of verapamil in a patient with compromised cardiac function, who recovered after the administration of intravenous calcium gluconate[30]; intravenous calcium solutions have proved effective in reversing other cases of verapamil toxicity.[31]

Contribution of norverapamil: Because it is formed by hepatic metabolism of the parent compound, norverapamil is not detected in plasma after intravenous bolus administration.[7] In our study long-term oral therapy resulted in plasma concentrations of norver-

pamil about equal to those of verapamil. Our observation that the ratio of norverapamil to verapamil remained unchanged over the therapeutic dose range of verapamil suggests that the metabolic conversion of verapamil to norverapamil is not concentration-dependent. Hence, measurement of norverapamil concentrations appears not to provide additional useful information in the management of patients with angina pectoris.

Clinical implications: Measurement of plasma drug levels may be helpful in the identification of patients who fail to respond to verapamil because of low plasma levels (less than 100 ng/ml), and hence may benefit from appropriate increases in the dose of the drug. Blood level determinations also appear important in the confirmation of iatrogenic or self-inflicted overdosage. Plasma verapamil levels cannot be used to predict the *individual* clinical responses in patients with angina pectoris.

Acknowledgment

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Long-Term Effectiveness of Verapamil in Stable and Unstable Angina Pectoris

One-Year Follow-Up of Patients Treated in Placebo-Controlled Double-Blind Randomized Clinical Trials

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The clinical responses to 12 months' treatment with verapamil were evaluated in 63 patients with stable and unstable angina pectoris in whom the effectiveness of verapamil had been established in short-term double-blind placebo-controlled randomized clinical trials.

In 41 patients with effort-related angina, long-term responses were sustained for periods exceeding 1 year. Twenty patients were evaluated by clinical history and showed a sustained reduction in frequency of anginal attacks and consumption of nitroglycerin with verapamil compared with the initial placebo control periods; the magnitude of this benefit was similar to that observed during double-blind treatment with the drug. Twenty-one patients were evaluated by serial treadmill exercise testing and showed a sustained improvement in exercise duration after 4, 8, 16, 24, and 52 weeks of verapamil treatment; withdrawal of the drug resulted in a deterioration of exercise performance to levels similar to those seen before initiation of therapy.

In 22 patients with unstable angina at rest, verapamil produced an amelioration of anginal symptoms that was sustained in most patients for longer than 1 year. However, these patients continued to have a high incidence of death and myocardial infarction in a frequency similar to that previously reported in large clinical studies using either combinations of verapamil and nitrates, nifedipine and propranolol, or propranolol and nitrates. Calcium-channel antagonists may decrease the number of patients requiring coronary artery bypass surgery for relief of refractory angina, but they do not appear to alter the natural history of the disease.

Verapamil has proved useful in the treatment of supraventricular tachyarrhythmias,[1,3] hypertrophic cardiomyopathy,[4–6] vasospastic or variant angina,[7] and chronic, stable, effort-induced angina.[8–13] Although several trials have confirmed the effectiveness of oral verapamil in patients with chronic stable angina pectoris, most trials have been of short duration, usually less than 4 to 6 weeks long. As a result, the long-term antianginal effects of verapamil and other calcium antagonists have not been well documented.

To evaluate the long-term value of verapamil in patients with ischemic heart disease, we conducted subjective and objective clinical follow-up examinations in 63 patients with stable and unstable angina pectoris, all of whom had been entered into short-term double-blind clinical trials comparing the effectiveness of verapamil with placebo or with propranolol; all were subsequently treated with verapamil for at least 1 year. Our results indicate that the beneficial effects of short-term therapy with verapamil are sustained during long-term treatment with the drug.

Long-Term Therapy of Stable Angina Pectoris

Methods

Patient population: The patient population was chosen from 66 patients with stable angina of effort who had participated in 3 randomized clinical trials. All patients had anginal pain on exertion relieved by rest or sublingual nitroglycerin, or both, occurring at least twice weekly for at least 4 weeks;

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TABLE I Long-Term Effects of Verapamil on Anginal Attack Frequency, Nitroglycerin Consumption, Heart Rate, and Blood Pressure

	Baseline Placebo	Double-Blind Verapamil	Double-Blind Placebo	Long-Term Follow-Up (Months After Conclusion of Double-Blind Phase) 1	2	4	6	8	10	12
Anginal attacks (per week)	11.7§ ±1.5	6.9*† ±1.7	19.4§ ±5.7	7.2*† ±2.6	7.9*‡ ±3.2	7.2*† ±2.9	7.6*† ±2.8	9.3*† ±3.7	7.4*† ±2.9	9.8*† ±4.0
Nitroglycerin tablets consumed (per week)	10.5§ ±1.8	7.1*† ±1.8	16.2§ ±5.4	6.7*† ±2.6	7.6*† ±3.2	7.0*† ±2.9	7.5*† ±2.8	9.2† ±3.7	7.1*† ±3.0	10.7 ±4.0
Heart rate (beats/min)	75.8 ±3.5	70.8 ±2.5	73.5 ±2.8	70.9 ±2.3	70.9 ±2.1	69.9*†§ ±2.7	65.0*†§ ±2.5	65.4*†§ ±2.7	66.2*†§ ±2.3	67.4*† ±2.5
Systolic blood pressure (mm Hg)	138.8§ ±5.6	122.9*† ±3.6	133.4§ ±4.0	126.5*† ±3.2	124.4*† ±3.9	127.8*† ±3.4	133.6§ ±3.8	131.3§ ±3.5	127.8* ±3.9	128.9*§ ±2.8
Diastolic blood pressure (mm Hg)	87.4§ ±2.7	75.2*† ±2.6	83.8§ ±2.9	73.0*† ±2.4	76.9*† ±2.0	75.1*† ±2.7	76.8*† ±2.2	75.6*† ±2.9	73.9*† ±2.7	73.7*† ±2.2

* $p < 0.05$ from baseline placebo; † $p < 0.05$ from double-blind placebo; § $p < 0.05$ from double-blind verapamil.
All values are means ± SEM

all patients demonstrated at least 1 mm S-T depression on two successive standardized treadmill exercise tests performed while receiving no treatment. No patient had severe hypertension or S-T segment changes while standing or during hyperventilation or during the Valsalva maneuver; none had unstable angina pectoris, acute myocardial infarction within 3 months, previous cardiac surgery, or congestive heart failure. No patient was taking digitalis, beta-adrenergic blocking drugs, long-acting nitrates, or antiarrhythmic agents before evaluation.

Trial protocol: All patients entered a randomized clinical trial comparing verapamil with either placebo or propranolol. Scheidt et al. (unpublished observations) entered 18 patients into a double-blind crossover trial comparing placebo with verapamil, given as either 320 or 480 mg daily depending on the results of an earlier single-blind dose titration phase; each drug was administered for 4 weeks. Frishman et al.[14] entered 20 patients into a double-blind crossover trial comparing verapamil (240 to 480 mg daily) with propranolol (60 to 320 mg daily); each drug was administered for 3 weeks. Bala Subramanian et al.[15] entered 28 patients into a double-blind crossover trial comparing verapamil 360 mg daily with placebo, each administered for 2 weeks.

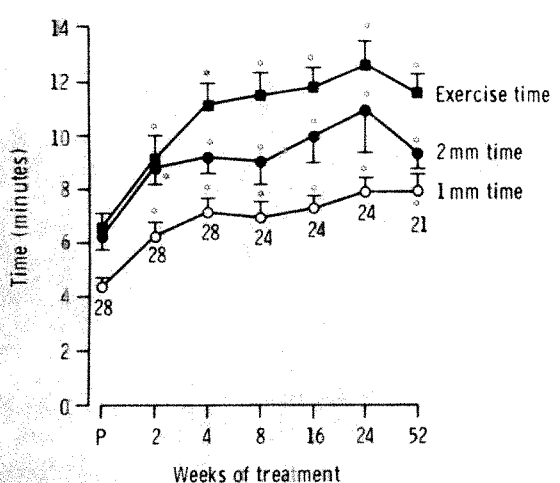

FIGURE 1. Effect of long-term treatment with verapamil on exercise time to the development of angina and to the appearance of 1 and 2 mm S-T segment depression. All values are mean values ± SEM. **Asterisks** indicate significant difference ($p < 0.001$) from placebo (P) control. The numbers under the graphs at each period indicate the number of patients studied. (Reproduced from Reference 15.)

At the end of the double-blind trial, each patient was considered for entry into a long-term verapamil follow-up protocol. Scheidt et al. entered 17 of their 18 patients into the long-term protocol; 1 patient died during the double-blind phase. Of these 17 patients, 2 failed to complete 1 year's treatment with verapamil for reasons unrelated to drug therapy: 1 because of compliance problems and 1 because of financial difficulties. Four patients received verapamil for 10 months with good results but did not complete 1 year's therapy at the time of termination of the long-term follow-up protocol. Of the 20 patients evaluated by Frishman et al., 8 patients chose to receive other therapy and 2 were considered unsuitable for long-term follow-up because of problems with compliance. The remaining 10 patients received verapamil for 12 months, but long-term data were obtained in only 9 patients; 1 patient who moved out of the state was lost to follow-up. As a result, Scheidt and Frishman followed up 20 patients on verapamil therapy for at least 1 year. There were 17 men and 3 women (age range 49 to 71 years). The doses administered (480 mg daily in 18 patients and 320 mg daily in 2 patients) were identical in each patient to those utilized during the double-blind studies.

All 28 patients evaluated by Bala Subramanian et al. were continued on long-term verapamil therapy. There were 25 men and 3 women (age range 43 to 69 years). The dose administered was 360 mg daily in each patient, identical to that utilized during the double-blind phase. All completed 4 weeks' treatment with verapamil; 4 patients were withdrawn before the 8 week evaluation because a dose of 360 mg daily of the drug could not be maintained: 1 because of first-degree heart block (0.28 second), 2 because of worsening angina (responsive to an increased dose of verapamil in 1 and to the addition of a beta-blocking drug in the other), and 1 because of an acute inferior myocardial infarction. Four patients were lost to follow-up study after 6 months of treatment; 21 patients completed 1 year's treatment with verapamil.

During the long-term follow-up period, verapamil was the only antianginal medication used. Long-acting nitrates and beta-blocking drugs were not added. Sublingual nitroglycerin was permitted during the study for relief of anginal attacks but was not used prophylactically. In addition, no patient was taking digitalis, diuretics, or antiarrhythmic agents.

Subjective and objective evaluations: All 41 patients were evaluated monthly for the first 2 months after completion of the double-blind phase, every second month until the

end of the first year, and every third month thereafter. The frequency of anginal attacks and consumption of nitroglycerin were determined from patient diaries, and heart rate and blood pressure were assessed at each return visit. Adverse effects were evaluated from a standardized questionnaire and by routine hematologic and biochemical laboratory tests.

In addition, the patients studied by Bala Subramanian et al.[15] underwent serial treadmill exercise testing after 4, 8, 16, 24, and 52 weeks of verapamil therapy. After completion of 1 year of treatment in these patients, verapamil was withdrawn; the dose was gradually reduced over 1 week and was replaced by placebo therapy for an additional 4 weeks. Treadmill testing was repeated at the end of the placebo period, and its results were compared with the exercise test during placebo treatment performed 1 year earlier. All tests were performed according to a protocol described previously[15] and were conducted 90 to 150 minutes after administration of the last dose of verapamil or placebo. Variables evaluated included the total duration of exercise and the duration of exercise until the appearance of 1 and 2 mm S-T depression.

Data analysis: The frequency of anginal attacks and nitroglycerin consumption were analyzed in the patients of Scheidt and Frishman only for the 20 patients who completed all evaluations during the entire 12 month follow-up period. Significance was determined by Wilcoxon signed rank t tests with each period compared with the baseline placebo, double-blind placebo, and double-blind verapamil phases. Exercise duration was assessed by Bala Subramanian et al. for 28 patients followed up for 4 weeks, 24 patients followed up to 6 months, and 21 patients followed up to 1 year; statistical analysis was performed by Student's paired t test. Group data are expressed as mean ± standard error of the mean (SEM).

Results

Anginal attack frequency and nitroglycerin consumption: In the 20 patients evaluated by Scheidt and Frishman, during the double-blind phases of the trial, verapamil reduced the number of anginal attacks from 19.4 ± 5.7 episodes per week on placebo to 6.9 ± 1.7 per week after 3 to 4 weeks on the drug ($p < 0.05$). During open-label verapamil therapy for 1 year, this improvement was sustained; the number of attacks throughout the follow-up period remained significantly smaller than observed during either the single- or double-blind placebo period (Table I).

During the double-blind phases of the trial, verapamil reduced the number of nitroglycerin tablets consumed from 16.2 ± 5.4 tablets per week on placebo to 7.1 ± 1.8 per week after 3 to 4 weeks of the drug ($p < 0.05$). During long-term open-label verapamil therapy, the number of nitroglycerin tablets consumed remained significantly smaller than that of either the single- or double-blind placebo period for the first 10 months (Table I). However, at 12 months nitroglycerin consumption was no longer significantly lower than the placebo baseline, but it was also not significantly higher than that observed during the first 4 months of verapamil therapy. These unusual findings at the 12 month follow-up visit are the result of enormous interindividual variation. Seventeen patients continued to have sustained responses; the number of anginal attacks and tablets of nitroglycerin consumed at 12 months remained similar to or below the mean of the preceding 6 observation periods. However, 3 patients had an increase in the frequency of anginal attacks between the 10th and 12th months of verapamil treatment (from 8.3 episodes per week on double-blind verapamil to 9.5 episodes per week during the initial 10 months' therapy and to 22.7 episodes per week at 12 months). One of these 3 patients had relief of angina after coronary artery bypass surgery; in the other 2, nifedipine was substituted for verapamil but without alteration in anginal frequency or nitroglycerin consumption.

Hemodynamic variables: In the 20 patients evaluated by Scheidt and Frishman, verapamil reduced systolic and diastolic blood pressure during double-blind therapy with the drug, and this reduction was sustained over the 12 month period in most patients. Diastolic blood pressure was more consistently reduced than was systolic pressure (Table I); diastolic pressure decreased from 83.8 ± 2.9 to 75.2 ± 2.6 mm Hg on verapamil (double-blind), and this reduction was sustained (73.7 ± 2.2 mm Hg) at 12 months. Heart rate was unchanged by verapamil therapy initially, but long-term treatment produced a progressive sustained modest decrease (from 76 to 67 beats/min) after 12 months. Two of the 3 patients who had an abrupt increase in the frequency of anginal attacks between 10 and 12 months also had an unexpected increase in blood pressure and heart rate at the time of this evaluation.

Treadmill exercise performance (Fig. 1): In the 28 patients evaluated by Bala Subramanian et al., the duration of exercise increased from 6.6 to 0.5 minutes on placebo to 9.2 ± 0.8 minutes after 2 weeks and to 11.4 ± 0.8 minutes after 4 weeks of verapamil therapy. This improvement was maintained during the 1 year follow-up period: 11.6, 11.8, 12.8, and 11.7 minutes after 8, 16, 24, and 52 weeks, respectively. The duration of exercise until the appearance of 1 and 2 mm S-T depression was prolonged after 2 weeks' treatment with verapamil, and this was sustained at repeat evaluation after 4 to 52 weeks.

All 28 patients had angina during the placebo period, but angina limited exercise in only 13 of the 28 verapamil-treated patients after 2 weeks and in only 8 of 24 treated patients after 4 weeks. No patient who became angina-free at 4 weeks had angina at 8, 16, 24, or 52 weeks of long-term verapamil therapy.

Seventeen of the 21 patients completing 1 year's treatment with verapamil agreed to have the drug withdrawn in order to assess its continued efficacy. Six of these 17 patients could not undergo repeat exercise testing; 3 had angina at rest, 1 had a marked increase in the frequency of anginal attacks, and 2 could not tolerate the recurrence of effort-related angina after 1 year. The mean exercise time in the 11 patients who underwent repeat treadmill evaluation was 6.9 ± 0.8 minutes, which was not significantly different from the values obtained in these patients during placebo therapy 1 year earlier (6.7 ± 0.5 minutes).

Adverse reactions: Of the 48 patients followed on verapamil for longer than 4 weeks, constipation was the most commonly noted adverse reaction, occurring in one third to one half of the patients evaluated. This was controlled by dietary adjustment or by laxatives in most

patients and resolved despite unchanged doses of verapamil and without any intervention in the others. Four patients had leg edema (bilateral in 2 and unilateral in 1) without signs of heart failure; edema was controlled by intermittent small doses of diuretic agents in all cases.

Seven patients exhibited cardiac rhythm disturbances. Two patients had junctional rhythms, accompanied by slight dizziness in 1 of them. Two patients had asymptomatic sinus bradycardia. One patient had atrial fibrillation with a slow ventricular response accompanied by mild dizziness; 2 patients had asymptomatic first-degree heart block. All symptoms and conduction disturbances disappeared when the dose of verapamil was reduced without a loss of antianginal efficacy.

One patient had acute urinary retention requiring bladder catheterization and subsequent transurethral prostatectomy; after surgery, he continued on verapamil therapy without further problems. Two patients reported occasional urinary frequency, which disappeared without dose adjustment. No significant hematologic or biochemical abnormalities were noted.

Verapamil therapy was not discontinued in any patient because of the development of adverse reactions.

Long-Term Therapy of Unstable Angina Pectoris

Methods

Patient population: The patient population consisted of 27 patients with unstable angina at rest who had participated in two randomized clinical trials. All patients had anginal pain at rest associated with electrocardiographic S-T segment elevation, depression, or both. Parodi et al.[16] evaluated 12 patients, aged 34 to 70 years; 7 had both exertional and rest angina, whereas the remaining 5 had only rest angina with preserved exercise tolerance. Obstructive coronary artery disease was confirmed in 8 of the 9 patients who underwent coronary arteriography. Mehta et al.[17,18] evaluated 15 patients, aged 42 to 80 years; 13 patients had both exertional and rest angina, whereas the remaining 2 had only angina at rest. All 12 patients who had coronary arteriography had significant obstructive coronary artery disease. No patient was taking beta-adrenergic blocking drugs during the period of evaluation.

Trial protocol: All patients entered a randomized clinical trial comparing verapamil with placebo. The study protocol of Parodi et al. consisted of a 2 day run-in period followed by four 2 day treatment periods alternating verapamil (480 mg daily) and placebo. The protocol of Mehta et al. employed a 24 hour placebo run-in period followed by randomization to either placebo or verapamil (320 mg daily); individual responses were determined at the end of each 24 hour period, with responders continuing on their effective regimen and nonresponders advancing from placebo to low-dose verapamil (320 mg daily) and from low-dose to high-dose verapamil (480 mg daily).

At the end of the double-blind trial, all patients were considered for long-term therapy with verapamil. All 12 patients evaluated by Parodi et al. were begun on long-term treatment, but only 10 patients were followed for a mean of 47 weeks; 2 were lost to follow-up. Only 12 of the 15 patients evaluated by Mehta et al. were started on long-term verapamil therapy: 1 had had a myocardial infarction during the double-blind trial, and 1 had failed to respond to verapamil therapy. Follow-up data are available for at least 12 months in all 12 patients and for up to 21 months in 6 patients.

During the long-term 1 year follow-up period, verapamil therapy was administered in doses identical to those found effective during the double-blind phase of the trial; these doses were altered only if patients had increasing angina (1 patient in whom the dose was increased from 480 to 640 mg daily) or notable side effects (constipation in 2 patients in whom the dose was decreased from 320 to 240 mg daily). Long-acting nitrates were utilized in 15 patients, but the doses utilized were similar to those administered in each patient before treatment with verapamil and remained unchanged during the period of follow-up. Concomitant therapy with beta-adrenergic blocking drugs was not employed. Sublingual nitroglycerin was permitted during the study for relief of anginal attacks but was not used prophylactically.

Long-term evaluation: All patients were evaluated periodically in terms of symptomatic status, specifically frequency of anginal attacks and number of nitroglycerin tablets consumed per week. Medical therapy was considered to have failed if patients had a myocardial infarction or angina unresponsive to increasing doses of verapamil, or died suddenly. Adverse effects of verapamil therapy were assessed at each clinical evaluation.

Results

Short- and long-term clinical results: In the 12 patients evaluated by Parodi et al.,[16] verapamil markedly reduced the number of symptomatic and asymptomatic episodes of S-T segment depression compared with placebo treatment. After completion of the short-term trial, 1 patient had a myocardial infarction while in the hospital, 8 were discharged from the hospital free of symptoms, and 3 others had occasional (1 to 3 episodes/week) attacks of angina on effort. Of the 10 patients who were followed up on long-term verapamil therapy, 7 remained free of pain and 3 continued to show a reduction in the number of ischemic episodes (averaging 2 per week).

Twelve of the 15 patients treated by Mehta et al.[17] had at least a 50% reduction in anginal attacks during short-term verapamil therapy, but these patients subsequently had a highly variable course.[18] Two of the 12 patients died within 1 week of discharge from the hospital, 1 with a myocardial infarction and another with sudden death. A third patient had an inferior wall myocardial infarction 2 weeks after discharge. Anginal frequency increased in 1 patient 1 month into follow-up despite increasing doses of verapamil (up to 640 mg daily), and therapy with the drug was discontinued. One patient was found to have left main coronary artery disease 6 months after discharge and underwent coronary artery bypass surgery, although he remained asymptomatic on verapamil. In general, symptomatic responses to verapamil were excellent, and the magnitude of effect seen after 1 week of therapy was maintained in most patients for the 12 month follow-up period (Fig. 2).

Seven patients were followed up by Mehta et al. for more than 1 year (up to 21 months). One patient had an

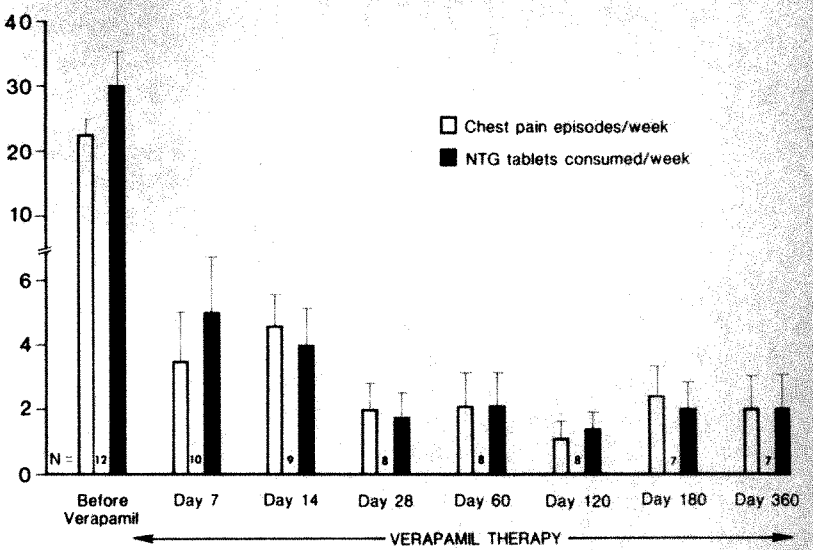

FIGURE 2. Weekly frequency (± SEM) of anginal episodes and nitroglycerin (NTG) consumption in 12 patients treated with verapamil on an ambulatory outpatient basis for 12 months. All 12 patients had responded to verapamil during the initial hospitalization. At the end of 12 months, 7 patients were still taking verapamil with good clinical responses.

uncomplicated inferior wall myocardial infarction at the end of 12 months' therapy with verapamil. The other 6 patients, however, continued to exhibit excellent symptomatic responses to verapamil therapy. Mean chest pain frequency in these 6 patients after 21 months' follow-up was 1.0 ± 0.6 episodes per week, and mean nitroglycerin consumption was 1.1 ± 0.5 tablets per week.

Adverse effects: Adverse reactions during long-term verapamil therapy were not reported in the patients treated by Parodi et al. Of the 12 patients followed up by Mehta et al., 7 had constipation, which was mild in 6 cases. P-R interval prolongation was observed in 4 patients, but only 1 of these had first-degree heart block, which was asymptomatic. The cardiothoracic ratio in all 12 patients remained unchanged during long-term verapamil therapy (47 ± 2% before and 46 ± 2% after verapamil). In 1 patient who failed to respond to verapamil, facial erythema developed at a dose of 640 mg daily; upon discontinuation of the drug, the erythema disappeared over 2 weeks.

Discussion

Verapamil is a calcium channel blocking agent which has been used for the treatment of stable and unstable angina pectoris for over a decade. Initial studies failed to demonstrate its efficacy in chronic stable angina,[8] but this was likely related to the small doses of verapamil administered (240 mg daily or less). Subsequent placebo-controlled double-blind studies using 320 to 480 mg daily demonstrated the short-term effectiveness of verapamil in stable angina pectoris for 4 to 8 weeks[9–13] and in unstable angina pectoris for 48 to 96 hours,[16,17] but few investigations have been conducted to show that these short-term benefits are sustained during long periods of drug administration.

The present report attempts to provide information concerning the long-term usefulness of verapamil therapy by reporting the follow-up results in patients who entered randomized clinical trials. Although such long-term data are not placebo-controlled, documentation of drug efficacy was confirmed initially by comparison with placebo-treated periods; therefore, maintenance of improvement during long-term verapamil treatment at levels similar to those achieved with verapamil during double-blind therapy can more confidently be attributed to the beneficial effects of the drug than if such long-term evaluations had not been preceded by a placebo-controlled drug response.

Long-term effectiveness in chronic stable angina: In patients with effort-related angina, verapamil reduced anginal attack frequency and nitroglycerin consumption when compared with treatment with placebo, and the magnitude of improvement seen during short-term treatment was sustained in most patients during long-term verapamil therapy. Only 3 of 41 patients followed up for at least 1 year exhibited an increase in anginal frequency on therapy, and these clinical exacerbations also failed to respond to therapy with alternative calcium channel blocking drugs. This sustained improvement was confirmed by standardized exercise testing; the prolongation of exercise time seen during short-term therapy was maintained after 1 year of verapamil treatment, and these benefits disappeared rapidly when the drug was withdrawn. The duration of exercise after withdrawal of verapamil for 1 year was similar to that seen during exercise testing before institution of the drug; this observation indicates that the sustained benefits of verapamil therapy were the result of drug treatment and were not due to an alteration in the national history of the disease.

Long-term effectiveness in unstable angina: Although a number of therapeutic modalities have been proposed for the treatment of patients with unstable angina associated with obstructive coronary artery disease, any short-term therapy may appear worthwhile

if placebo controls are not used, since many patients with unstable angina have a spontaneous remission of symptoms.[19] On other hand, uncontrolled observations during long-term therapy often prove inconclusive since the ambulatory course of the disease varies from the in-hospital course, and a large number of patients continue to have ischemic episodes despite optimal medical therapy and often require coronary bypass surgery for relief of symptoms; myocardial infarction and sudden death also occur with a variable frequency.[20] In the 22 patients followed up long-term in the present study, verapamil proved effective compared with placebo in the short-term relief of symptoms in each patient. Although this clinical improvement was generally well maintained, myocardial infarction and sudden death continued to occur; coronary artery bypass surgery, however, was not performed for relief of symptoms in any patient.

These results are similar to the more extensive but uncontrolled observations of Severi et al.,[21] who treated 120 patients with angina at rest accompanied by S-T segment elevation with verapamil and nitrates for 2 to 8 years. The improvement in anginal symptoms observed in most patients was sustained during the follow-up period; only 12% of patients had an exacerbation of anginal symptoms during long-term verapamil therapy, and 50% of patients became completely pain-free by the fourth year of follow-up. Despite these symptomatic benefits, however, these patients had a high incidence of myocardial infarction and death (22% and 5%, respectively, within 1 year). These results are remarkably similar to those obtained in a double-blind trial reported by Gerstenblith et al.,[22] who found that nifedipine reduced the number of patients who required coronary artery bypass surgery for relief of anginal symptoms, but failed to alter the number of patients who had myocardial infarction or died (16 and 7%, respectively, within 4 months); furthermore, benefits were limited to those patients with S-T segment elevation during episodes of pain. The incidence of myocardial infarction and death in the series of Severi et al. and the study by Gerstenblith et al. are similar to those described in the National Cooperative Study Group comparison of medical (propranolol and nitrates) and surgical therapy.[20] However, in contrast to the experience with calcium antagonists, a large proportion (40%) of patients treated with propranolol and nitrates subsequently had severe angina poorly responsive to medical therapy. Therefore, calcium antagonists appear to reduce the number of patients who require bypass surgery for relief of angina but do not appear to alter the the frequency of myocardial infarction and death.

Safety of long-term verapamil therapy: Verapamil was very well tolerated in the 63 patients we followed up for longer than 1 year. The most common adverse reaction was constipation; this was usually readily responsive to change in diet or mild laxatives. Conduction system disturbances were occasionally seen, but these were usually asymptomatic and responded to a reduction in the dose of verapamil. The peripheral edema noted in a few patients was relieved by the intermittent use of diuretics.

We did not observe potentially serious adverse reactions of verapamil therapy (hypotension, congestive heart failure, or hepatotoxicity) in any of our patients, even though rare instances have been reported by other investigators.[23–25] The incidence of these reactions appears very low and should not deter clinicians from using verapamil as a safe and effective long-term antianginal drug.

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Comparative Effects of Abrupt Withdrawal of Propranolol and Verapamil in Angina Pectoris

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The potential hazards of abrupt withdrawal of propranolol have been described in patients with angina pectoris; however, the effects of abrupt withdrawal from long-term therapy with verapamil have not previously been investigated. The comparative effects of withdrawal from long-term treatment with propranolol and verapamil were assessed in a placebo-controlled double-blind randomized crossover study of 20 patients with stable angina pectoris. Patients received placebo for 2 weeks, then increasing doses of propranolol (60 to 320 mg/day) or verapamil (240 to 480 mg/day) for 3 weeks. Patients were then abruptly withdrawn from drug onto placebo for 1 week, followed by crossover to the other drug treatment and a second withdrawal period.

All 20 patients were withdrawn from verapamil without evidence of a rebound increase in frequency of anginal attacks, blood pressure, heart rate, or rate-pressure product and without a rebound deterioration in exercise tolerance. In contrast, with propranolol withdrawal, 2 patients (with the highest baseline angina attack rate) had a severe exacerbation of their anginal syndrome and could not undergo formal exercise testing; the other 18 patients were withdrawn from propranolol without incident. Plasma catecholamines were increased during exercise compared with rest during all treatments; however, the levels of catecholamines during exercise were significantly higher with propranolol than with verapamil and placebo ($p < 0.05$). Levels of exercise catecholamines returned to placebo baseline values after withdrawal of propranolol.

Increased severity of angina pectoris, supraventricular and ventricular arrhythmias, myocardial infarction, and sudden death have been reported in patients with ischemic heart disease who are abruptly withdrawn from long-term oral therapy with propranolol.[1-4] Little information is available concerning the exact frequency and mechanism of these propranolol withdrawal phenomena, although the possibility of sympathetic hypersensitivity has received the most interest.[5,6] Other explanations include progression of underlying coronary artery disease,[3] enhanced platelet aggregation,[7] increased triiodothyronine levels,[8] alterations in plasma renin activity,[3] or continued high levels of physical activity despite withdrawal of propranolol.[3]

Calcium-channel antagonists are now considered important modalities in the management of patients with ischemic heart disease[9] and supraventricular arrhythmia.[10] However, despite their increasing clinical use, little is known regarding the effects of abrupt treatment withdrawal from these medications.

We recently reported the results of a placebo-controlled double-blind randomized crossover trial that compared the antianginal effectiveness of long-term oral therapy with propranolol and verapamil in patients with angina pectoris.[11] Using data obtained from this same trial, we now report on the comparative effects of abrupt withdrawal from long-term treatment with verapamil and propranolol.

Methods

Subjects: The study group consisted of 20 ambulatory patients (19 men and 1 woman) whose characteristics were described in our original report.[11] Each patient had a primary diagnosis of chronic stable angina for at least 3 months before enrollment. At least 3 attacks of angina per week were required for entry; each patient also demonstrated an abnormal response on 2 occasions to a multistage treadmill exercise test with at least 1 mm of flat or downward-sloping S-T segment depression 0.08 second after the J point. All patients signed an informed consent form approved by the Committee on Clinical Investigations of the Albert Einstein College of

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TABLE I Effects of Placebo, Large-Dose Propranolol and Verapamil Therapy, and Treatment Withdrawals on Resting Heart Rate (HR), Blood Pressure (BP), and Rate-Pressure Product in Patients with Angina Pectoris (n = 20)

	Placebo Baseline (Week 2)	Propranolol (320 mg/day)	Propranolol Withdrawal	Verapamil (480 mg/day)	Verapamil Withdrawal
			Supine		
Heart rate (beats/min)	75.7 ± 14.8	59.6 ± 7.3*	74.7 ± 11.7	80.5 ± 15.2	79.2 ± 15.4
Systolic BP (mm Hg)	151.5 ± 25.7	139.4 ± 15.7	126.7 ± 17.4*	146.2 ± 14.4	146.9 ± 23.2
Diastolic BP (mm Hg)	90.6 ± 10.7	83.4 ± 11.1†	77.0 ± 11.3*	93.3 ± 12.8	90.4 ± 14.4
Rate-pressure product (HR × SBP/10^2) (beats mm Hg/min)	113.9 ± 26.4	82.8 ± 11.3*	95.1 ± 22.7†	117.6 ± 25.5	117.1 ± 32.1
			Standing		
Heart rate (beats/min)	85.5 ± 17.7	61.6 ± 8.7*	88.0 ± 15.2	72.9 ± 12.0†	81.9 ± 14.0
Systolic BP (mm Hg)	148.5 ± 20.5	139.5 ± 20.0	146.7 ± 14.8	132.6 ± 18.8†	142.8 ± 23.6
Diastolic BP (mm Hg)	93.6 ± 11.4	89.5 ± 12.7	95.5 ± 13.4	83.5 ± 11.2†	88.9 ± 13.0
Rate-pressure product (HR × SBP/10^2) beats mm Hg/min	126.6 ± 29.2	85.7 ± 16.3	129.4 ± 27.2	97.0 ± 23.2	118.0 ± 31.0

* Compared with placebo baselines $p < 0.01$. † Compared with placebo baselines $p < 0.05$.
SBP = systolic blood pressure.

Medicine. Patients were excluded on the basis of criteria that we previously described.[11]

Study design: The study protocol followed a placebo-controlled double-blind randomized crossover design.[11] Briefly, it consisted of an initial 2-week single-blind placebo run-in phase, during which time each patient received a placebo verapamil tablet (identical to an 80 mg tablet) and a placebo propranolol capsule (identical to an opaque gelatin capsule used throughout the study) every 8 hours. Thereafter, each patient received increasing doses of verapamil (240 mg/day, 80 mg every 8 hours; 320 mg/day, 80 mg every 6 hours; and 480 mg/day, 120 mg every 6 hours) or propranolol (60 mg/day, 20 mg every 8 hours; 160 mg/day, 40 mg every 6 hours; and 320 mg/day, 80 mg every 6 hours) over a 3 week titration period. After the initial dose titration, the patients underwent a 3 day down-titration phase, during which the amount of medication was decreased approximately 33% per day. The patients then entered a 5 to 7 day placebo period. After completion of this second placebo period, each patient crossed over to the other medication regimen, and the dose-titration, down-titration, and placebo phases were repeated.

Methods of observation: The patients were seen every week after entering the first-dose titration period. Daily diaries were reviewed and consumption of nitroglycerin tablets and study medications was assessed. Supine and standing heart rate and blood pressure were measured at each visit. Exercise tests were performed and blood levels of propranolol, verapamil, and norverapamil[12,13] were determined during the placebo period, during each dose-titration stage, and after withdrawal.

Exercise protocol: The exercise protocol followed that described by Bruce.[11,14] Each test was analyzed for heart rate, systolic blood pressure, rate-pressure product, and S-T segment displacement achieved at maximal effort, as well as total exercise duration. Exercise work was calculated as previously described.[11]

Plasma catecholamine levels: Blood samples for plasma catecholamine levels were obtained in a subgroup of 10 patients during rest in the supine and standing positions and at the end point of maximal upright treadmill exercise. Determinations were made during placebo baseline, on maximal propranolol and verapamil therapy, and 1 week after treatment withdrawals. Samples of blood were obtained from an indwelling venous catheter with a minimum of patient stimulation and collected in chilled tubes containing ethyleneglycol-bis(beta-amino-ethyl ether) N,N′-tetraacetic acid (EGTA) and reduced glutathione. The samples were immediately spun, and the plasma was separated and frozen at −20° C. The samples were coded and the plasma epinephrine and norepinephrine levels measured with use of a single isotope-derivative technique.[15]

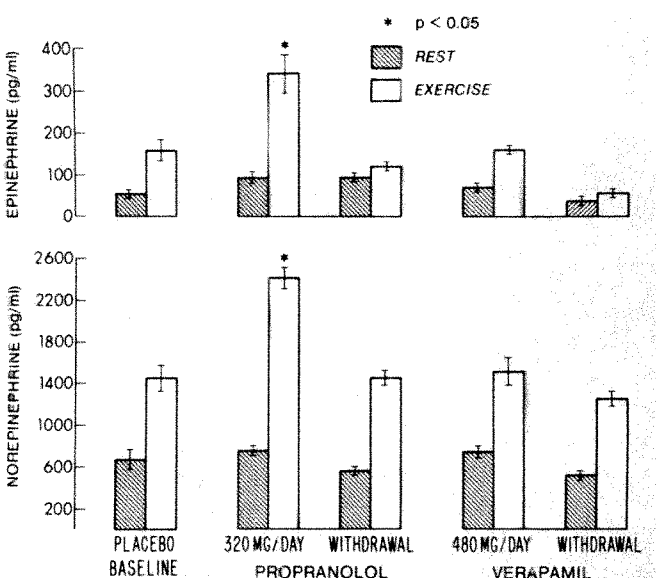

FIGURE 1. The effects of placebo, high-dose propranolol, high-dose verapamil, and their treatment withdrawal on plasma epinephrine and norepinephrine levels obtained at rest (standing) and at maximal exercise (standing). The increase in plasma catecholamines from rest to exercise is significant during all treatment periods. **Asterisks** indicate a significant difference between values on active drug therapy compared with values during administration of placebo.

Statistical analysis: All results are reported as means ±1 standard deviation except in Figure 1, where the standard

TABLE II Effects of Placebo, Large-Dose Verapamil and Propranolol Treatment, and Treatment Withdrawals on Frequency of Anginal Attacks and Nitroglycerin (NTG) Consumption, Exercise Tolerance and Work, and Determinants of Myocardial Oxygen Consumption (n = 20)

	Baseline Placebo	Propranolol (320 mg/day)	Propranolol Withdrawal	Verapamil (480 mg/day)	Verapamil Withdrawal
			Angina Results		
Attacks/week	7.1 ± 11.4	5.8 ± 9.6	10.1 ± 12.6	3.9 ± 7.6*	4.6 ± 4.5
NTG consumption/week	5.5 ± 16.8	3.8 ± 9.0	6.8 ± 11.8	2.9 ± 7.7†	3.8 ± 5.0
			Stress Test Results		
Exercise duration (s)	313.7 ± 98.7	431.7 ± 114.7*	328.0 ± 98.1	464.7 ± 123.7*	366.0 ± 114.2
Exercise work (kpm/10^3)	2.6 ± 1.3	4.3 ± 2.2*	2.8 ± 1.3	4.7 ± 2.2*	3.3 ± 1.4
ECG S-T segment at end-exercise (mm)	−2.0 ± 1.3	−1.6 ± 1.6	−1.6 ± 1.0	−1.6 ± 1.1	−2.0 ± 1.5
Peak systolic BP (mm Hg)	178.8 ± 32.2	150.8 ± 26.5*	167.7 ± 31.8	159.4 ± 26.4†	167.7 ± 30.8
Peak diastolic BP (mm Hg)	99.1 ± 13.0	88.2 ± 14.1	96.7 ± 26.5	88.4 ± 15.2†	95.8 ± 16.8
Peak heart rate (beats/min)	135.6 ± 18.4	102.7 ± 17.1*	137.7 ± 18.3	126.3 ± 21.2	131.4 ± 18.0
Peak rate-pressure product (HR × SBP/10^2) (beats mm Hg/min)	245.5 ± 59.7	157.8 ± 46.9*	231.8 ± 63.8	199.8 ± 53.7†	227.9 ± 50.1

* Compared with placebo baselines $p < 0.01$. † Compared with placebo baselines $p < 0.05$.
ECG = electrocardiogram; other abbreviation as in Table I.

error of the mean is used as the index of dispersion. In comparing the effects of each drug and treatment withdrawal with placebo baseline, a modified Fisher least significant difference test was employed after one-way analysis of variance yielded a significant result. Differences were considered significant if the p value was less than 0.05.

Results

Patients: All 20 patients who entered the study were successfully titrated to doses of 320 mg/day of propranolol and 480 mg/day of verapamil. Drug compliance (determined by medication counts) for the placebo baseline, two-drug treatment, and two withdrawal phases (placebo) was 98 ± 10%. Plasma drug levels confirmed patient compliance, since a linear relation between dose and plasma level was observed. One week after active therapy was withdrawn, there was no trace of either drug in the blood.

All 20 patients were withdrawn from long-term therapy with verapamil and underwent exercise without evidence of deterioration from placebo baseline status. Eighteen patients were withdrawn from propranolol without difficulty; however, the 2 remaining patients who had the most severe angina at the start of the study, exhibited ischemic changes at rest on the electrocardiogram one week after therapy with propranolol was withdrawn, and could not undergo formal exercise testing during the final visit of the study. No patient in either treatment group had an acute infarction during the withdrawal periods.

Effects on resting and exercise blood pressure and heart rate (Tables I and II): Compared with the placebo baseline, both verapamil and propranolol therapy lowered the standing heart rate at rest and decreased systolic pressure, heart rate, and the rate-pressure product during exercise. After withdrawal of both verapamil and propranolol, there was a return of mean resting heart rate and exercise-induced changes in heart rate, blood pressure, and rate-pressure product toward baseline values without evidence of rebound hemodynamic changes. Hemodynamic variables after abrupt withdrawal of verapamil were similar to their placebo baseline values; after withdrawal of propranolol, supine systolic and diastolic blood pressures were lower than their values during placebo therapy ($p < 0.01$).

Effects on angina pectoris and nitroglycerin consumption (Table II): Subjectively, all 20 patients experienced relief of symptoms with both propranolol and verapamil compared with placebo. After the withdrawal of verapamil, the frequency of anginal attacks returned toward their placebo values without evidence of rebound effects. After withdrawal of propranolol, there was a slight but insignificant increase in anginal attacks and nitroglycerin consumption from placebo baseline values. However, 2 patients exhibited ischemia at rest after withdrawal of propranolol; no patient did after withdrawal of verapamil.

Effects on exercise tolerance and work, and the exercise electrocardiogram (Table II): Compared with placebo, both propranolol and verapamil increased the duration of treadmill exercise time and work ($p < 0.01$). After withdrawal of both verapamil and propranolol treatment, there was a return of exercise tolerance toward baseline. During placebo therapy, 4 of the 20 patients had ventricular ectopy at peak exercise, which was reduced by both propranolol and verapamil, but returned without exacerbation after each treatment withdrawal.

Effects on plasma catecholamines (Fig. 1): With exercise, there was a significant increase in both plasma epinephrine and norepinephrine levels compared with resting values ($p < 0.01$). Compared with placebo, there was no difference in the effect of verapamil on plasma catecholamine levels recorded at rest and exercise. With propranolol, there was no change in resting plasma catecholamine levels; however, during exercise there was a significant increase in plasma epinephrine and nor-

epinephrine determinations compared with exercise levels during treatment with placebo and verapamil ($p < 0.05$). After withdrawal of verapamil and propranolol, rest and exercise catecholamine levels returned to placebo baseline values.

Discussion

Many cardiovascular drugs used to alter left ventricular preload and afterload, or the function of the sympathetic nervous system activate compensatory physiologic mechanisms, and the abrupt withdrawal of some of these drugs has been reported to cause adverse rebound withdrawal phenomena.[16–18] Abrupt withdrawal of propranolol, clonidine, and nitroprusside can produce deleterious rebound effects that suggest excessive sympathetic activity.[1–3,19,20] However, other cardiovascular drugs cause both reflex and end-organ receptor readjustments, and yet do not produce rebound phenomena when therapy is abruptly withdrawn.[21,22] The effects of abrupt withrawal from long-term therapy with calcium-channel blocking agents have not previously been elucidated.

Propranolol withdrawal: With propranolol, a nonselective beta-adrenergic blocking agent, withdrawal effects in patients with coronary artery disease include accelerated angina pectoris, myocardial infarction, ventricular arrhythmias, and sudden death.[1,2] Only a small percentage of patients with coronary artery disease and stable angina pectoris will experience problems after sudden cessation of propranolol therapy[3]; this effect appears most marked in patients in whom propranolol is withdrawn before open-heart surgical procedures.[23] Usually, the patients with angina pectoris who exhibit the greatest benefit from propranolol are those most likely to exhibit symptomatic rebound reactions when the drug is withdrawn.[1–3]

Long-term therapy with propranolol has been shown to increase the number of beta-adrenergic receptors in animals and human volunteers[18]; hence, it has been hypothesized that withdrawal symptoms are secondary to the residual increase in the number of beta-adrenergic receptors that occurs when propranolol is no longer present in the body.[3,16] Hypersensitivity to adrenergic stimulation after propranolol withdrawal has been demonstrated in normal and hypertensive human subjects.[5,6,24] This sensitivity to exogenous catecholamines appears to be greatest by the sixth day after abrupt withdrawal of propranolol, at a time when the drug has disappeared from the plasma.[6]

In our double-blind study, all 20 patients were withdrawn from long-term therapy with propranolol, 320 mg/day, placed on placebo, and evaluated 7 days later. Although there were no myocardial infarctions, 2 patients with the most severe angina at study entry experienced rebound phenomena on propranolol withdrawal and could not undergo exercise testing because of resting electrocardiographic abnormalities; these 2 patients did not have this reaction after verapamil withdrawal. The remaining 18 patients were withdrawn from propranolol and verapamil without a deterioration from the placebo baseline status. However, we found little evidence of an adrenergic hypersensitivity phenomenon in any patient after treatment withdrawal. Plasma catecholamines, which were elevated during exercise with propranolol therapy, returned to placebo baseline levels 1 week after withdrawal; heart rate and blood pressure, at rest and during exercise, returned toward placebo baseline values without evidence of rebound hemodynamic changes. Our findings are in agreement with those of other investigators who found only a small percentage of patients manifesting problems after abrupt cessation of propranolol therapy.[1,2] The lack of greater withdrawal effects with propranolol in this study might reflect a withdrawal period that was too short, a prolonged action of the drug despite its short plasma half-life,[25] the actions of active metabolites,[25] or a training effect.

Verapamil withdrawal: The cardiovascular effects that follow abrupt withdrawal a long-term therapy with calcium-channel antagonists have not been systematically investigated. There have been only rare individual case reports describing rebound phenomena in patients abruptly withdrawn from long-term verapamil therapy.[26] However, rebound phenomena were not observed when patients with vasospastic angina,[27] unstable angina,[28] and systemic hypertension[29] were withdrawn from verapamil and given placebo as part of the protocol of controlled clinical trials. In contrast, rebound phenomena are frequently observed when propranolol is abruptly discontinued during the performance of placebo-controlled trials.[2] In the present double-blind controlled study, all 20 patients with stable angina pectoris were withdrawn from long-term therapy with verapamil, 480 mg/day, and given placebo without an exacerbation of angina pectoris in any patient. After verapamil withdrawal, there was a return of anginal symptoms, exercise performance, and hemodynamic responses toward placebo baseline values with no evidence of rebound events. The lack of withdrawal effects with verapamil might, however, reflect a withdrawal period that was too short, a prolonged action of the drug despite its short plasma half-life,[30] the actions of active metabolites,[30] or a training effect.

An interesting finding in this study was the absence of any effect on plasma catecholamine levels at rest and during exercise with verapamil treatment. Vasodilator therapy in hypertension is usually associated with an activation of the sympathetic nervous system in response to the decrease in systemic resistance.[31] In this study, verapamil caused less sympathetic discharge for similar levels of exercise than did propranolol. No differences were observed in the effects of placebo, verapamil, and verapamil withdrawal on levels of plasma norepinephrine and epinephrine measured at rest and during exercise. This atypical sympathetic response to vasodilator therapy may be the result of verapamil's actions on the slow calcium channel; calcium may be important in the release of catecholamines from the adrenal medulla, and verapamil may inhibit this release.[32–34] Accordingly, the antianginal and antiarrhythmic effects of verapamil may be mediated in part by an inhibition or reduced rate of catecholamine re-

lease in human beings. It appears that although propranolol blocks beta-adrenergic stimulation by catecholamines at the receptor level, verapamil may reduce the catecholamine response to exercise.

Clinical implications: Problems with abrupt withdrawal of long-term therapy with propranolol in patients with angina pectoris (not undergoing surgery) are uncommon and appear unrelated to heightened adrenergic activity. Caution should still be exercised when attempting to withdraw patients with angina from this treatment procedure, especially before surgery. There appear to be no adverse reactions after withdrawal of long-term verapamil treatment; however, further investigations need to be done to confirm these early observations.

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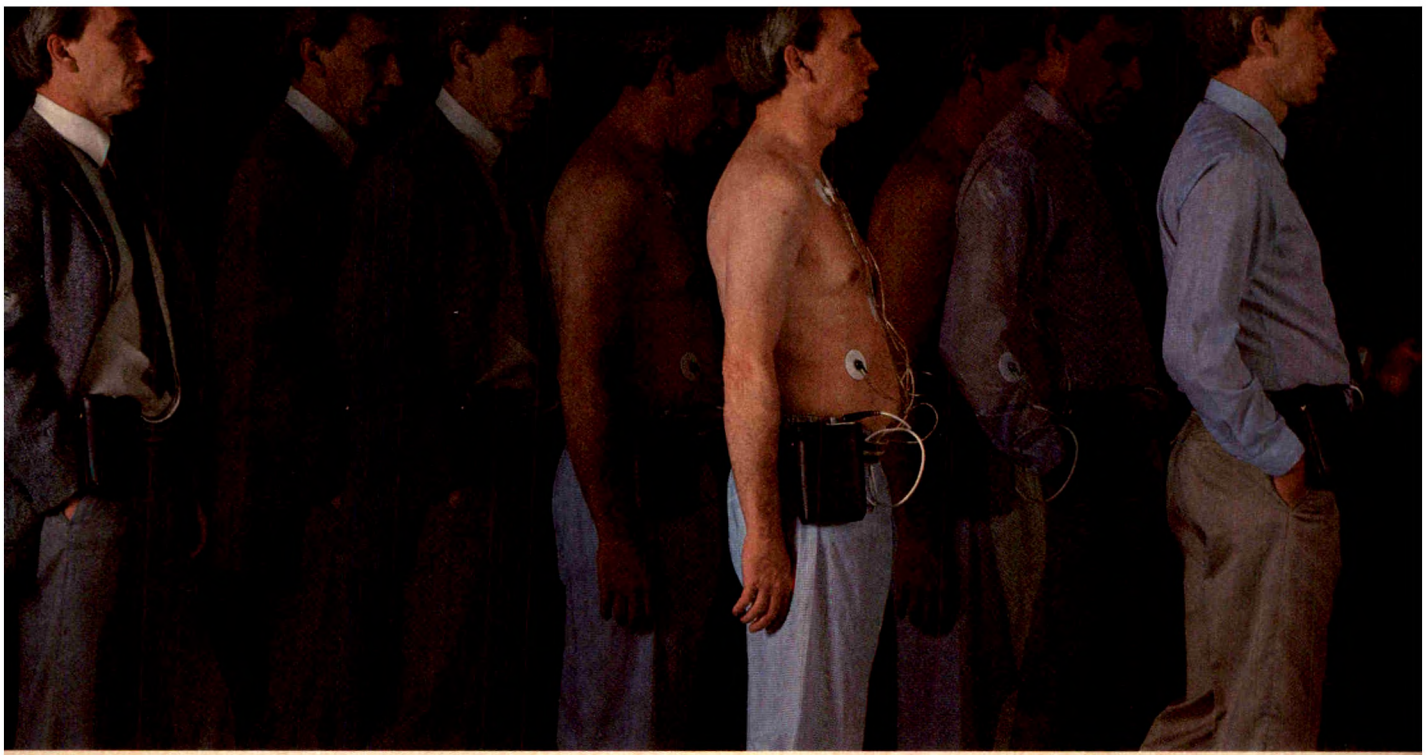

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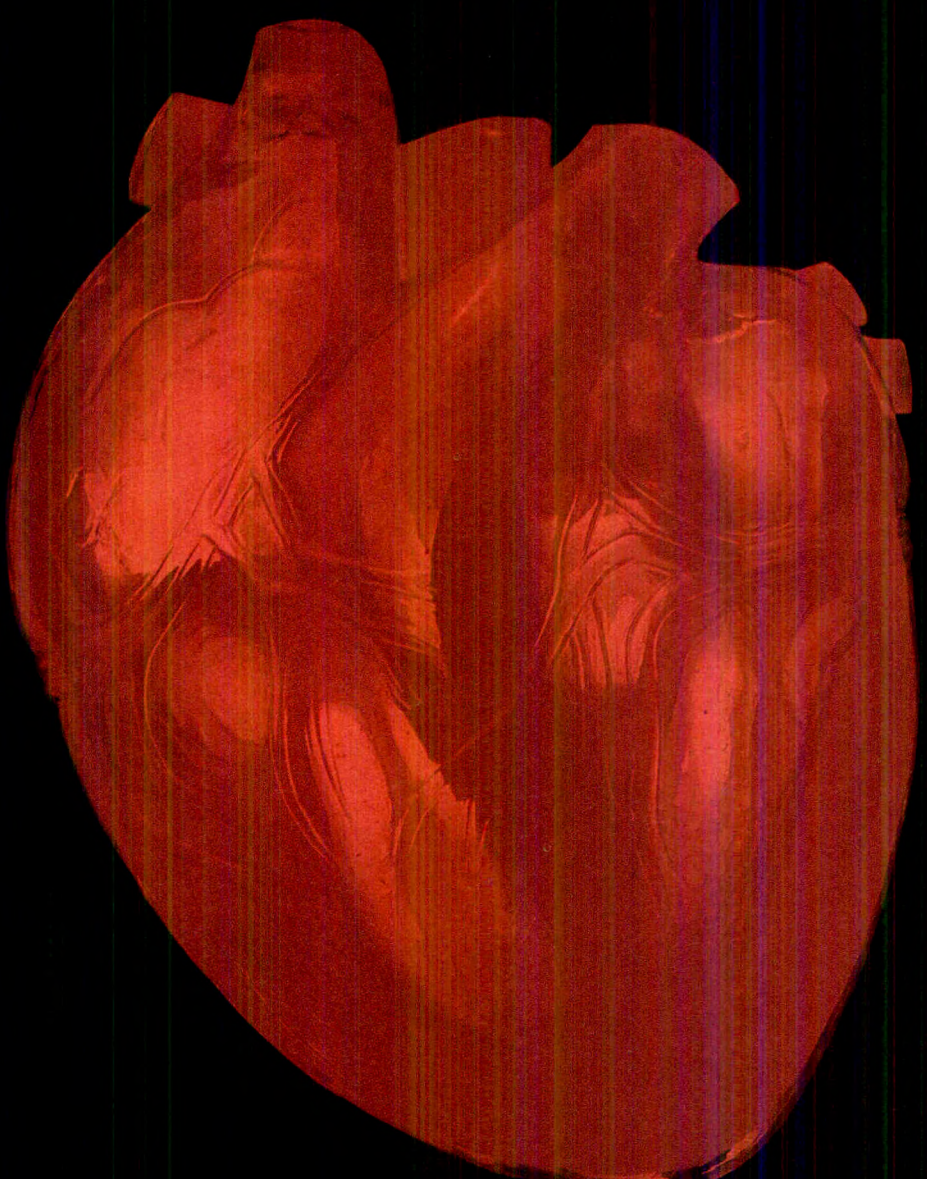

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- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias.
- Atrial and ventricular ectopic arrhythmias.

In the A-V sequential (DVI) mode, the Model 7000 may have application in the following:

- Sick Sinus Syndrome (sinus bradycardia, sinus arrest, SA block, and the brady-tachy syndrome).
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias.
- Atrial and ventricular ectopic arrhythmias.

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Contraindications

General. There are no known contraindications to the use of pacing as a therapeutic modality for control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implantation procedure used by the physician.

DDD Mode. The DDD mode is contraindicated in the presence of atrial fibrillation, atrial flutter and rapid atrial rhythms of slow retrograde conduction.

DVI Mode. In the DVI mode, atrial pacing is ineffective in the presence of chronic atrial fibrillation or flutter.

Warnings

Diathermy. Diathermy should not be used on patients with pacemakers because of possible heating effects in the pulse generator and at the implant site. Electrosurgical units should never be used in the presence of unipolar pulse generators because of the danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead.

Defibrillation. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. See the specific precautions and warnings in the technical manuals included with the pulse generator.

Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

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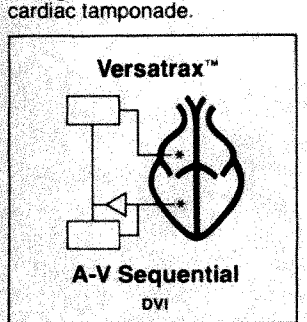

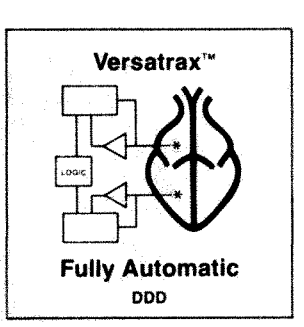

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LETTERS*

DEFINITION OF VENTRICULAR TACHYCARDIA

The careful and meticulously analyzed study by Bigger et al.,[1] while undoubtedly of value in further characterization of postinfarction ventricular tachycardia (VT), starts with an unfortunate choice of definitions and channels its discussion to the hardly novel "clinical implication" that "VT may be the harbinger of subsequent arrhythmic death."

To define VT as the authors did—as 3 consecutive complexes of ventricular origin regardless of their rate—would include ventricular escape rhythms, including those produced by electrical pacemakers. The authors' definition is at variance with the standard electrocardiographic nomenclature over the past several decades.[2–4] The only "justification" for this appears to be a similar mortality observed for rates above and below 100 beats/min. This may be spurious, since there is no way of knowing how the patients actually died with respect to the authors' subdivision.

The implication about subsequent arrhythmic death is similarly unwarranted, given that the *observed* 1,370 episodes of VT behaved rather innocuously at the time of the recording. Their predictive value is further weakened by the reported lack of quantitative relation between the frequency of VT and subsequent death in individual patients. Furthermore, the rarity of the R-on-T phenomenon in this series and its frequency in the cases of sudden death observed outside hospital[5,6] tend to imply different arrhythmic mechanisms at the time of actual sudden death.

The strong predictive indexes of sudden death, namely the left ventricular contraction abnormalities and the anatomy of the coronary artery disease,[7,8] are substituted by the somewhat imprecise category of clinical left ventricular failure, presumably present in 29% of the authors' patients, for comparison with the predictive value of VT. The case for the independent predictive value of VT in this setting has yet to be made.

George Nikolic, MB, BS, FRACP, Woden, Australia

1. **Bigger JT, Weld FM, Rolnitzky LM.** Prevalence, characteristics and significance of ventricular tachycardia (three or more complexes) detected with ambulatory electrocardiographic recording in the late hospital phase of acute myocardial infarction. Am J Cardiol 1981;48:815–823.
2. Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Boston: Little, Brown 1973: 34.
3. Tenth Bethesda Conference on Optimal Electrocardiography of the American College of Cardiology. Task Force I: Standardization of Terminology and Interpretation. Am J Cardiol 1978;41:130–145.
4. WHO/ISC Task Force: Definition of Terms Related to Cardiac Rhythm. Am Heart J 1978;95:796–806.
5. **Nikolic G, Bishop RL, Singh JB.** Sudden death recorded during Holter monitoring. Circulation 1982;66:218–225.
6. **Adgey AA, Devlin JE, Webb SW, Mulholland HC.** Initiation of ventricular fibrillation outside hospital in patients with acute ischaemic heart disease. Br Heart J 1982;47: 55–61.
7. **Geltman EM, Ehsani AA, Campbell MK, Schechtman K, Roberts R, Sobel BE.** The influence of location and extent of myocardial infarction on long-term ventricular dysrhythmia and mortality. Circulation 1979;60:805–814.
8. **Califf RM, Burks JM, Behar VS, Margolis JR, Wagner GS.** Relationships among ventricular arrhythmias, coronary artery disease and angiographic and electrocardiographic indicators of myocardial fibrosis. Circulation 1978;57:725–730.

REPLY: We appreciate Dr. Nikolic's interest in ventricular arrhythmias occurring in the late hospital phase of acute myocardial infarction. His comments indicate dissatisfaction with our current knowledge in this area and a desire to have answers to many unresolved questions. We share his interest in these matters. Dr. Nikolic posed questions about 3 issues raised in our report on ventricular tachycardia (VT): (1) our definition of VT, (2) the hypothesis that the presence of VT in a predischarge Holter recording may indicate future *arrhythmic* death, and (3) the relation between VT and other functional risk predictors, especially left ventricular dysfunction. All of these are controversial and worthy of discussion.

Definition of VT: VT has been variously defined in terms of the number of consecutive ventricular premature depolarizations and the rate. Although the modal electrocardiographic definition for VT is three or more consecutive ventricular premature depolarizations, definitions requiring 4 or 5 consecutive ventricular complexes are still used by some workers. Clinical electrophysiologists often use 5 or 10 consecutive ventricular premature depolarizations in response to progammed ventricular stimulation as a definition of nonsustained VT. Also, the rate requirement in the definition of VT varies; the 3 most common in order of frequency of use are 100 beats/min, 120 beats/min, and any rate.[1,2] Our decision a priori to include all *spontaneous* episodes of 3 or more consecutive ventricular premature depolarizations in our study was made because of the total ignorance about the prevalence, characteristics, and significance of VT in the late hospital phase of myocardial infarction when we began our study. We anticipated that we might find some justification for a rate component in the definition of VT by examining the relation between the average VT rate and subsequent clinical events (see Figure 1B in our report). In this analysis, 2 interesting facts emerged. First, the interectopic interval in an episode of VT often is extremely variable. Second, there is not yet *any hint* of a relation between the rate of an episode of consecutive ventricular premature depolarizations and mortality. A study by Kleiger et al.[3] took an approach similar to ours. To avoid the semantic problem of using the term *tachycardia* for episodes with rates less than 100 beats/min, they chose the term *ventricular runs*. This addresses the issue in an intelligent way, permitting continuing studies of ventricular arrhythmias without aggravating traditional definitions. Very large studies will be needed to resolve the questions about the significance of various characteristics of ventricular runs. We would encourage investigators to keep data on a full range of rates to enhance our knowledge in an area where there is a great void.

Implications about mechanisms of death: This is another difficult and controversial topic. Epidemiologists are frustrated in their attempts to classify deaths in a functional, that is, mechanistic sense. At present, the fact that death has occurred, the time between symptoms and death, and the cardiac or noncardiac nature of death are the mainstays of classification. Attempts to attribute death to ischemia, left ventricular power failure, or arrhythmias are fraught with difficulty because of data available at the time of death and because of complex interrelations among these functional entities. In our section on clinical implications, we discussed the *hypothesis* that VT may predict *arrhythmic death* but emphasized that the complex interactions among functional risk factors make alternative hypotheses tenable. Also, we discussed how to gather information about the interactions and how to use it in managing patients at present. We also are frustrated by the limitations in classifying postinfarction deaths and encourage efforts to advance the state of the art.[4,5]

Relation between VT and other risk factors: This is one of the most difficult issues raised by Dr. Nikolic since the studies to date, including our own, are so small. Dissection of the relations among VT, ischemia, left ventricular dysfunction, and death requires a large effort and has not yet been achieved.[1,6–8] First, a study with a large number of patients with VT and a large number of deaths is needed; about 100 of each would be desirable. The sample should be unbiased, that is, representative. Second, acceptable measures for ischemia, left ventricular dysfunction, and VT are needed. Finally, an accurate assessment of death in functional terms is needed. Our current hypothesis about what might be found in such a study is that VT would be significantly and importantly related to left ventricular dysfunction and significantly less so to ischemia. In addition, adjusting for these interactions, VT would have a significant and important association with cardiac death in the year after myocardial infarction. We are not at all certain that VT would be more strongly associated with "arrhythmic death" than other modes of death, if, indeed, the functional mode of death can be identified with sufficient precision.

J. Thomas Bigger, Jr., MD, Francis M. Weld, MD, and Linda M. Rolnitzky, MS, New York, New York

* Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

1. **Bigger JT Jr, Dresdale RJ, Heissenbuttel RH, Weld FM, Wit AL.** Ventricular arrhythmias in ischemic heart disease: mechanisms, prevalence, significance and management. Prog Cardiovasc Dis 1977;19:255–300.
2. **Lown B, Fakhro AM, Hood WB Jr, Thorne GW.** The coronary care unit. New perspectives and directions. JAMA 1967;199:188–193.
3. **Kleiger RE, Miller JP, Thanavaro S, Province MA, Martin TF, Oliver GC.** Relationship between clinical features of acute myocardial infarction and ventricular runs 2 weeks to 1 year after infarction. Circulation 1981;63:64–69.
4. **Hinkle LE, Thaler HT.** Clinical classification of cardiac deaths. Circulation 1982;65: 457–464.
5. **Moss AJ, Marcus FI, Griffith LSC, Edwards JE.** Categorization of the mechanism of cardiac death in patients with coronary heart disease. Circulation (in press).
6. **Anderson KP, DeCamilla J, Moss AJ.** Clinical significance of ventricular tachycardia (3 beats or longer) detected during ambulatory monitoring after myocardial infarction. Circulation 1978;57:890–897.
7. **Moller M, Lyager-Nielsen B, Fabricus J.** Paroxysmal ventricular tachycardia during repeated 24-hour ambulatory electrocardiographic monitoring of postmyocardial infarction patients. Br Heart J 1980;43:447–453.
8. **Bigger JT Jr, Weld FM, Rolnitzky LM.** Prevalence, characteristics and significance of ventricular tachycardia (three or more complexes) detected with ambulatory electrocardiographic recording in the late hospital phase of acute myocardial infarction. Am J Cardiol 1981;48:815–823.

CARDIOLOCUTION AND DYSRHYTHMIA

The epithet *cardiolocution* which appears in the title of Spodick's editorial[1] neatly exemplifies the very problem he discusses. *Cardiolocution* is truly a neologism,* a coined word, in this instance one of known provenance. It is a nonce word, created for the occasion—cute perhaps, but unnecessary and ephemeral. It is a neat irony that this term precedes an editorial in which the author uses his scientific knowledge, extensive vocabulary, and concern for language† as a kind of multiheaded missile to attack the linguistically accurate *dysrhythmia* and to defend the indefensible *arrhythmia*.

Dysrhythmia has more than the virtue of ringing right, as Spodick agrees, cheerfully damning with faint praise. Etymologically, it accurately describes the medical condition that the cardiac rhythm is disturbed. The generally accepted but inaccurate *arrhythmia* does not conform with classic Greek usage, as an article in the *British Heart Journal*[2] claimed some years ago. To the word-sensitive physician or patient, it suggests, erroneously and humorously, if one has a taste for such humor, that rhythm has ceased. *Dorland's*, of course, in its Analytical Word List, defines the prefix *a* as a "negative prefix" and *dys* as a prefix meaning "bad or improper." I need not list sample medical terms in which these prefixes are correctly used.

I have written to medical editors, publishers, authors, and pharmaceutical houses to urge the use of "dysrhythmia," in the interest not merely of linguistic purity but also of medical accuracy. My correspondence is available for your perusal. As a result, Parke-Davis has changed its advertising, and now uses the term *dysrhythmia*. Searle will do so, and others are contemplating changing.

Philip R. Trommer, MD, Philadelphia, Pennsylvania

1. **Spodick DH.** Cardiolocution. The cardiologist's assault on English. Am J Cardiol 1981;48:973–974.
2. **Krikler D.** What to call arrhythmias? Br Heart J 1978;40:1325–1326.

REPLY: Two cheers for Dr. Trommer. *Cardiolocution* is indeed a nonce word, created for the occasion. I did not use it in the text and I will not use it again—nor do I expect it to enter our vocabulary. Other writers have used terms such as *Medispeak*, and in my editorial I referred to George Orwell, who created the words *newspeak* and *doublethink*. Orwell is highly regarded for these creations and they, like *cardiolocution*, were never intended for general use.

Trommer has exercised himself mightily over the issue of *arrhythmia* versus *dysrhythmia*. This was a microscopic part of my message and I attributed it to the distinguished editor of the *British Heart Journal* (who is the genuine Greek scholar), as Trommer recognized. Trommer caught the words but missed the spirit of that part of my essay, summarized in its last sentence: "All these examples of medical jargon are linguistically unattractive but not really harmful because their meaning remains intact and no physician will be misled by them." Indeed, this was only an introduction to the subsequent material which embodied my real aims. Finally, the fact that Trommer cites advertisers who employ—or, perhaps more accurately, *deploy*—certain language is hardly an endorsement of its accuracy.

Trommer's definition of *neologism*, cited from *Dorland's*, is too clever by half. That is only one—and not the principal—definition of *neologism*, as Trommer ought to know. We all have enough Greek to know that it literally means "new word," and *Stedman's Medical Dictionary* gives "a new word or phrase, or an old word used in a new sense," as its *first* definition. Furthermore, since even for medical communication the best English should be intelligible to the layman, *Webster's Third New International Dictionary*, on page 1516, gives its *first* definition of *neologism* as "a new word, usage or expression."

On second thought, only one cheer for Dr. Trommer.

David H. Spodick, MD, DSc, Worcester, Massachusetts

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* *Neologism* is defined as "a meaningless word uttered by a psychotic or delirious person" by *Dorland's Illustrated Medical Dictionary*.

† An erudite and scholarly article on the subject is entitled "Medical Language, An Exclusive Code," by Nicholas P. Christy, published in Transactions & Studies of the College of Physicians of Philadelphia, Series 5, Vol 3, No. 4, Dec. 1981:301–311. He also fully discusses Orwell.

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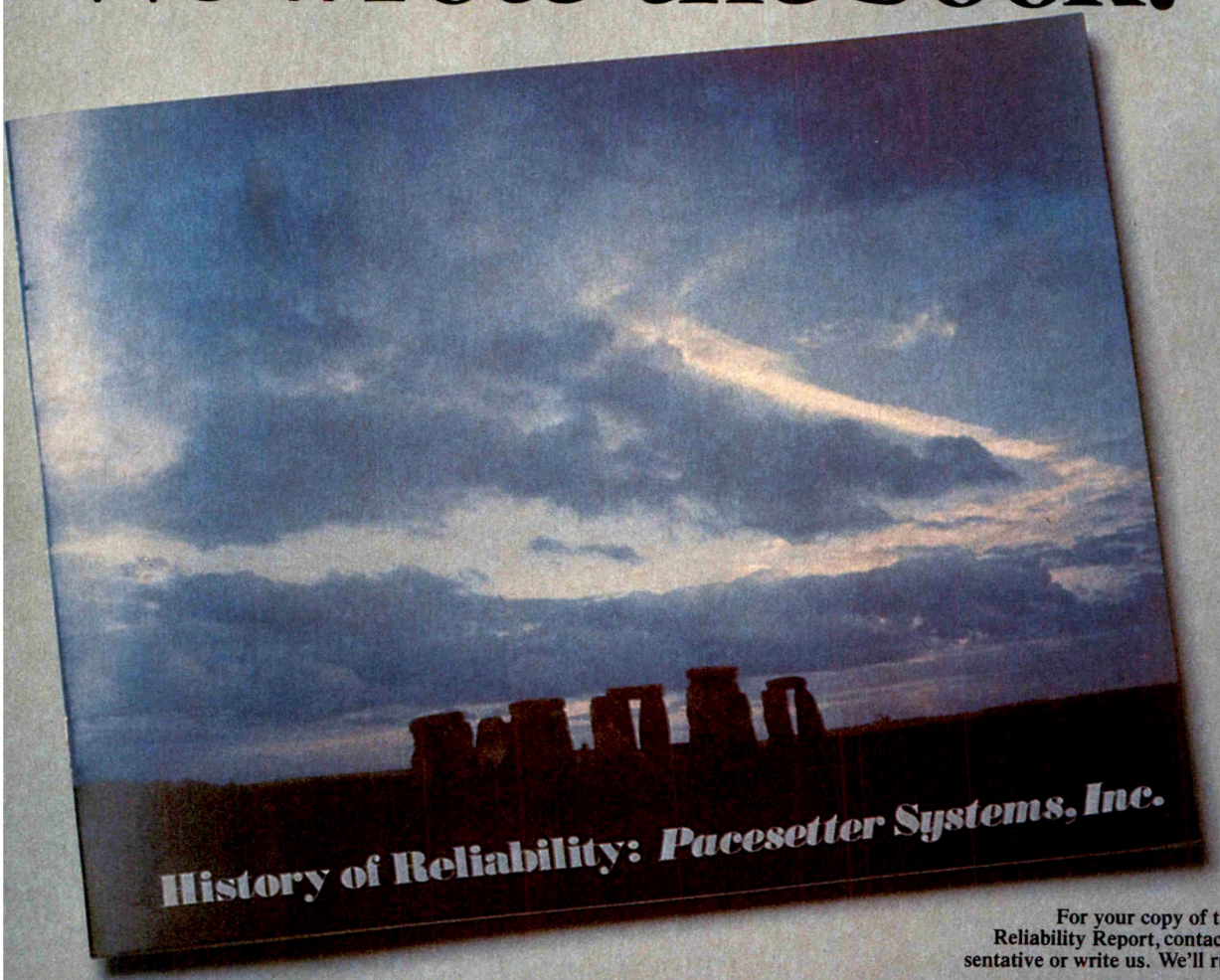

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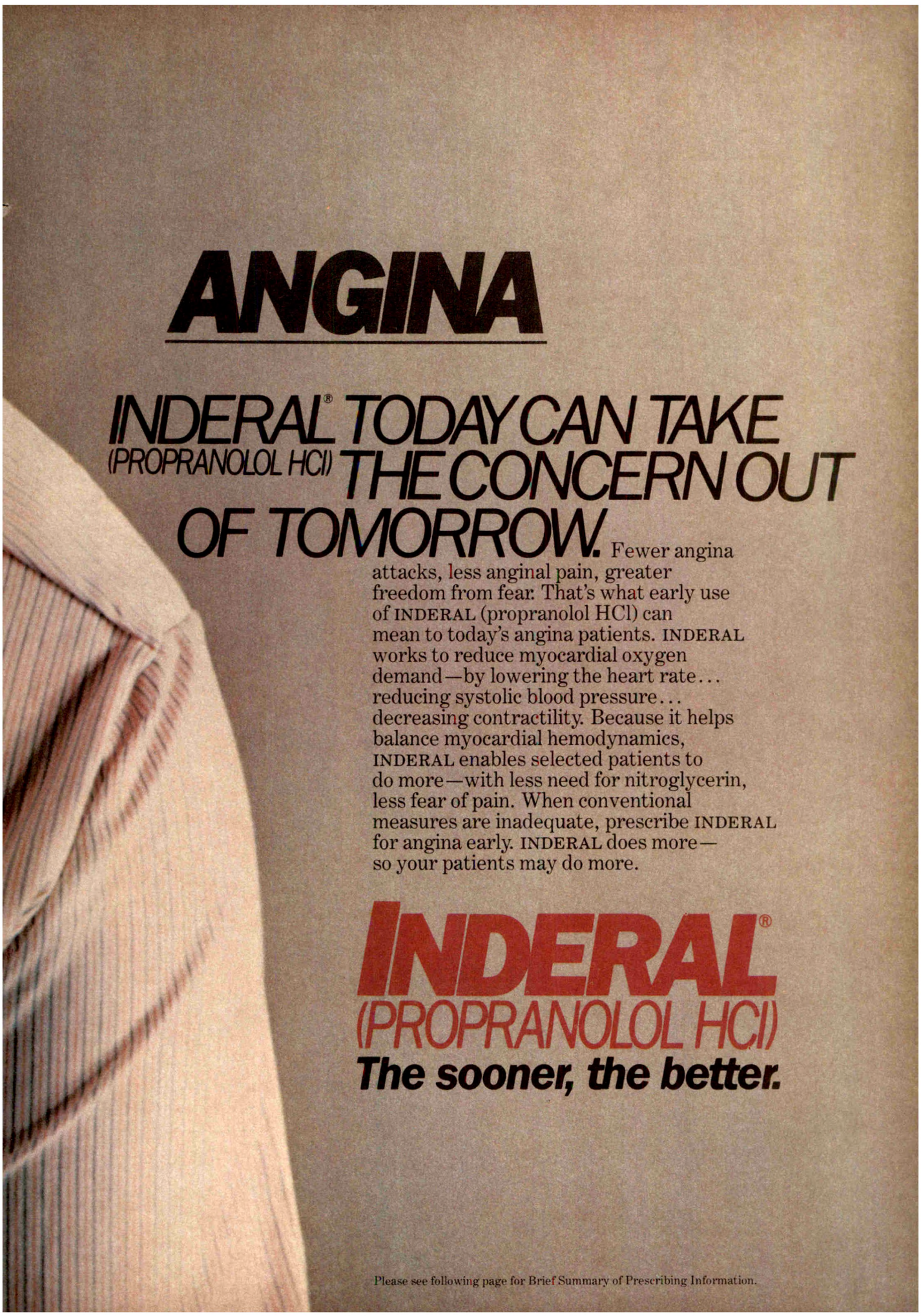
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WARNINGS

CARDIAC FAILURE. In congestive heart failure, inhibition with beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In patients already receiving digitalis, propranolol may reduce the positive inotropic action of digitalis and may have an additive depressant effect on AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, in rare instances, cardiac failure has developed during propranolol therapy. At the first sign of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and observed closely. a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Give special consideration to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol should be withdrawn slowly, since abrupt withdrawal may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta-blockade impairs the ability of the heart to respond to reflex stimuli. Except in pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery. In case of emergency surgery, the effects of propranolol can be reversed by administration of beta-receptor agonists such as isoproterenol or levarterenol, but such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), administer with caution, since propranolol may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA. Propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in patients with labile diabetes. A precipitous elevation of blood pressure may accompany hypoglycemic attacks.

USE IN PREGNANCY. Safe use in human pregnancy not established. Embryotoxic effects have been seen in animals at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if propranolol is administered, since it may occasionally produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

Observe laboratory parameters at regular intervals. Use with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System*: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal*: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic*: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory*: bronchospasm. *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous*: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta-blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings*: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

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—Each hexagonal-shaped, green, scored tablet is embossed with an "I" and imprinted with "INDERAL 40," contains 40 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0424-81) and 1,000 (NDC 0046-0424-91). Also in unit dose package of 100 (NDC 0046-0424-99).

—Each hexagonal-shaped, yellow, scored tablet is embossed with an "I" and imprinted with "INDERAL 80," contains 80 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0428-81) and 1,000 (NDC 0046-0428-91). Also in unit dose package of 100 (NDC 0046-0428-99).

The appearance of these tablets is a trademark of Ayerst Laboratories.

Store at room temperature (approximately 25° C).

INJECTABLE

—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).

Store at room temperature (approximately 25° C).

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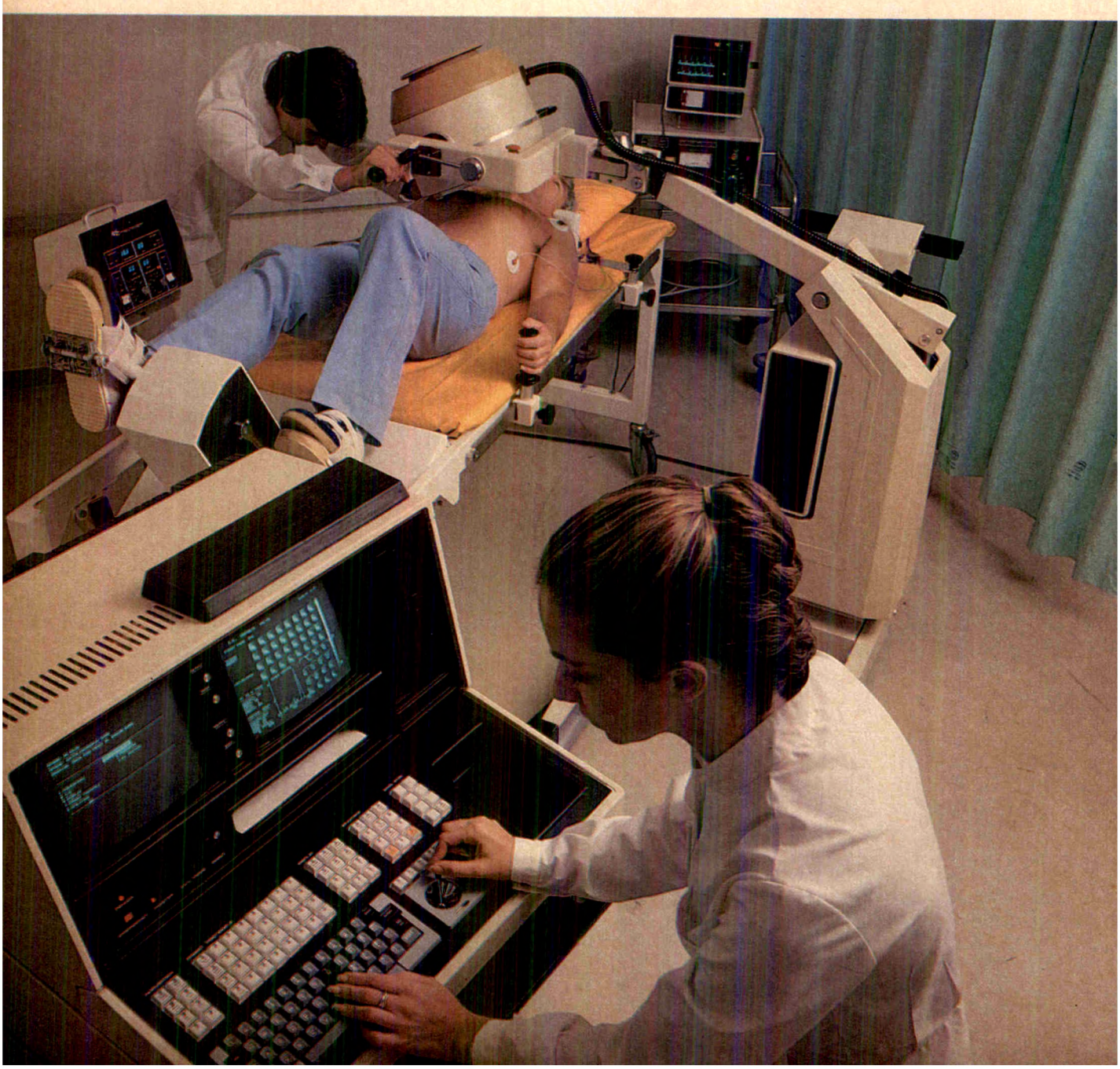

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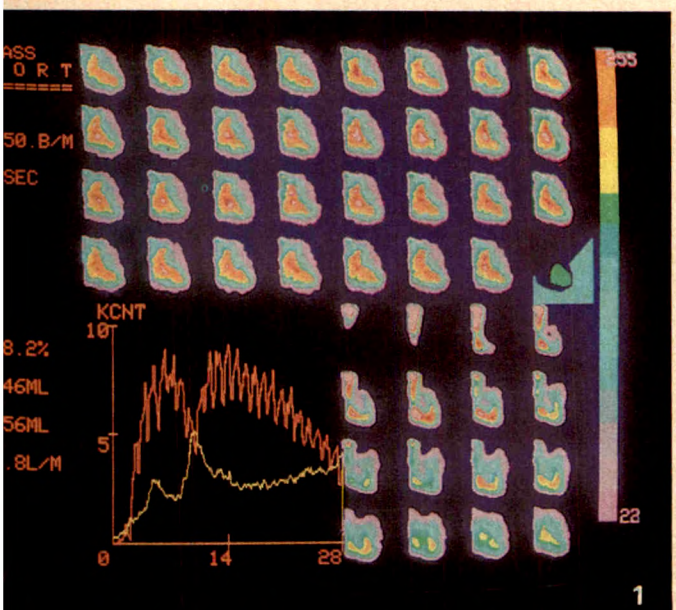

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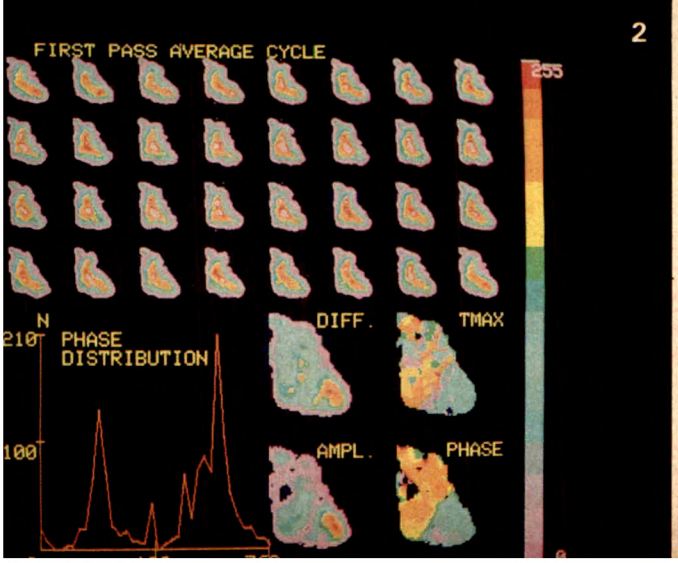
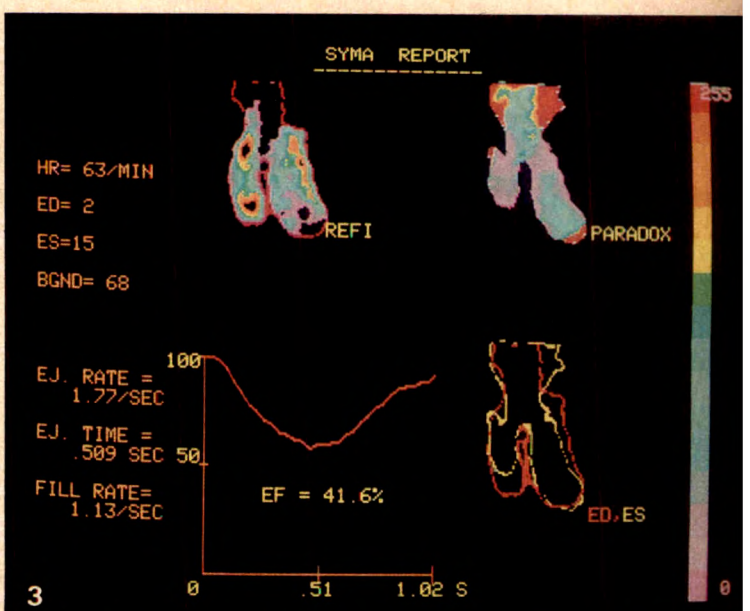


2

Photos 1 & 2: Apex 215M's high count rates enable superior definitive first-pass studies. Typical of its capabilities are global and regional ventricular function analysis and direct quantification through volume.



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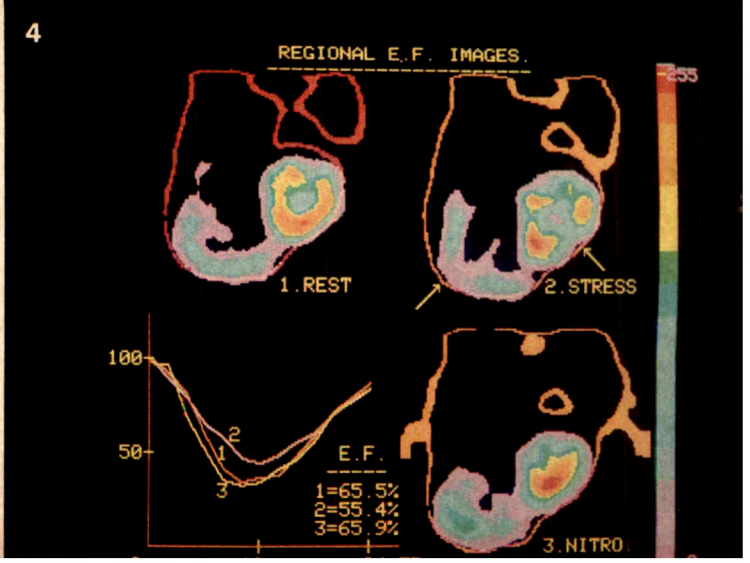
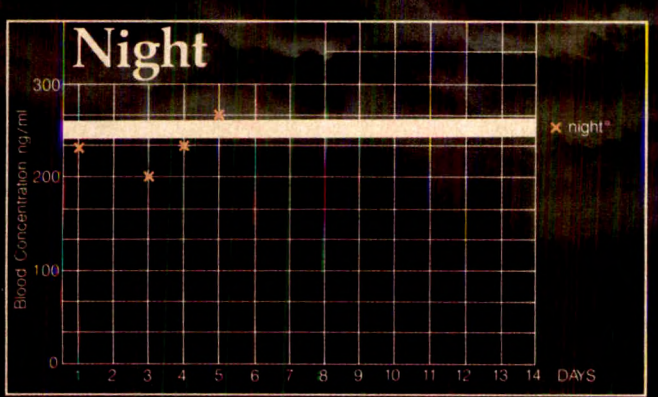


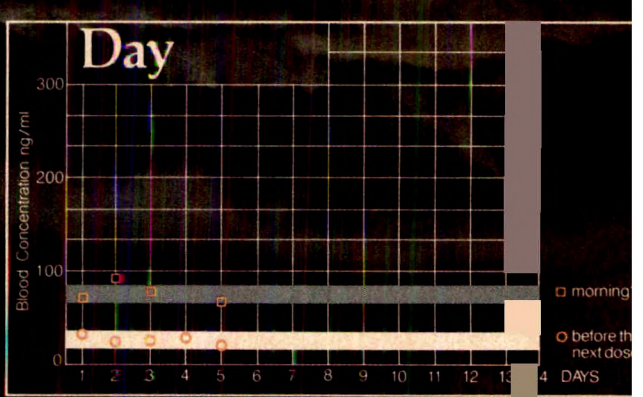
4

Photos 3 & 4: Apex 215M can clearly display various global and regional functions on a single image monitor. In these examples, ventricular functions in a resting heart appear above; the lower image compares the resting heart with two different intervention situations.

The difference between night...

RESTORIL® (temazepam) blood levels after consecutive nightly 30-mg doses[1,2]





RESTORIL® (temazepam): Effective at night—little residual daytime medication—patients awake alert and refreshed

The half-life of RESTORIL (temazepam) parallels normal sleep time. In contrast, the major active metabolite of flurazepam has a 65-hour mean half-life. With RESTORIL therapy, a major portion of active material is cleared by early morning—enabling patients to awake alert and refreshed.

No significant impairment of daytime activities

In double-blind, placebo-controlled studies,[3,4] no detectable impairment in cognitive function or motor coordination occurred in patients who had taken a 30-mg dose of RESTORIL (temazepam) the night before. In the same studies, poorer performance scores were attained by patients who had taken a 30-mg dose of flurazepam prior to bedtime.

Patients receiving benzodiazepines should be cautioned about possible combined effects with alcohol and other CNS depressan and about operating machinery or driving a vehicle after ingesting the drug.

Sleep time and quality significantly improved

In 21 double-blind studies[5] involving 1,221 adult patients (508 of whom received RESTORIL capsules), RESTORIL therapy prove highly effective from the first night of administration. RESTORIL (temazepam) is indicated for the relief of insomnia associated wit the complaints of difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakenings from the first nigh REM sleep remained essentially unchanged. Patients reported a significant improvement in the general quality of sleep.

*night: 3 hours after a nightly 30-mg dose. †morning: 12 hours after a nightly 30-mg dose. ‡before the next dose: 24 hours after a nightly 30-mg dose

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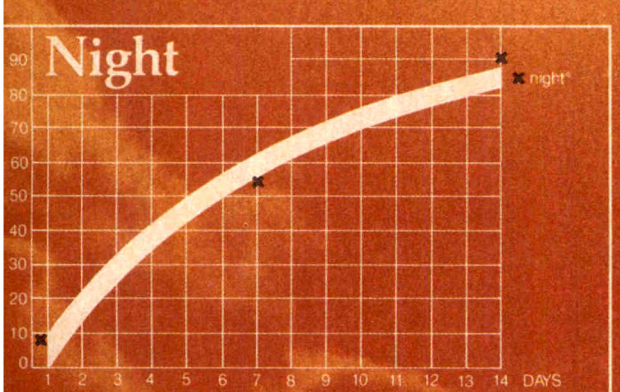
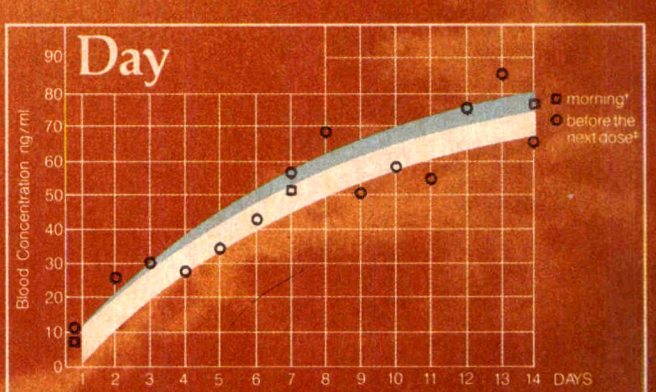
and day.

ood levels of the major active metabolite of Dalmane® C IV[1] after consecutive nightly 30-mg doses[6]





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One 15-mg capsule, h.s.—*recommended initial dosage for elderly and/or debilitated patients.*

INDICATIONS AND USAGE: Restoril® (temazepam) is indicated for the relief of insomnia associated with complaints of difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Since insomnia is often transient and intermittent, the prolonged administration of Restoril is generally not necessary or recommended. Restoril has been employed for sleep maintenance for up to 35 consecutive nights of drug administration in sleep laboratory studies.

The possibility that the insomnia may be related to a condition for which there is more specific treatment, should be considered.

CONTRAINDICATIONS: Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Also, ingestion of therapeutic doses of benzodiazepine hypnotics during the last weeks of pregnancy has resulted in neonatal CNS depression. Restoril is contraindicated in pregnant women. Consider a possibility of pregnancy when instituting therapy or whether patient intends to become pregnant.

WARNINGS: Patients receiving Restoril (temazepam) should be cautioned about possible combined effects with alcohol and other CNS depressants.

PRECAUTIONS: In elderly and/or debilitated patients, it is recommended that initial dosage be limited to 15 mg. The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression; it should be recognized that suicidal tendencies may be present and protective measures may be necessary.

If Restoril is to be combined with other drugs having known hypnotic properties or CNS-depressant effects, due consideration should be given to potential additive effects.

Information for Patients: Patients receiving Restoril should be cautioned about possible combined effects with alcohol and other CNS depressants. Patients should be cautioned not to operate machinery or drive a motor vehicle. They should be advised of the possibility of disturbed nocturnal sleep for the first or second night after discontinuing the drug.

Laboratory Tests: The usual precautions should be observed in patients with impaired renal or hepatic function. Abnormal liver function tests as well as blood dyscrasias have been reported with benzodiazepines.

Pregnancy: Pregnancy Category X. See Contraindications.

Pediatric Use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS: The most common adverse reactions were drowsiness, dizziness and lethargy. Other side effects include confusion, euphoria and relaxed feeling. Less commonly reported were weakness, anorexia and diarrhea. Rarely reported were tremor, ataxia, lack of concentration, loss of equilibrium, falling and palpitations. And rarely reported were hallucinations, horizontal nystagmus and paradoxical reactions, including excitement, stimulation and hyperactivity.

Restoril is a controlled substance in Schedule IV. Caution must be exercised in addiction-prone individuals or those who might increase dosage.

DOSAGE AND ADMINISTRATION: *Adults:* 30 mg usual dosage before retiring; 15 mg may suffice in some. *Elderly and/or debilitated:* 15 mg recommended initially until individual response is determined.

SUPPLIED: Restoril (temazepam) capsules—15 mg maroon and pink, imprinted "RESTORIL 15 mg"; 30 mg, maroon and blue, imprinted "RESTORIL 30 mg". Packages of 100, 500 and ControlPak® packages of 25 capsules (continuous reverse-numbered roll of sealed blisters). SDZ1-159

Before prescribing, see package insert for full product information.

References:

1. Schwarz HJ: Br J Clin Pharmacol *8*:23s, 1979: Mean of 7 patients through 5 days of therapy projected to 14 days. Data on file indicate that steady-state values for plasma concentrations are reached by day 2 or 3.
2. Sleep lab studies on patients who received RESTORIL capsules for up to 27 consecutive nights indicate that steady-state plasma concentrations are achieved by the second or third night. Data on file, Sandoz Pharmaceuticals.
3. Pishkin V, et al: J Clin Psychiatry *41*:358, 1980.
4. Roth T, et al: Br J Clin Pharmacol *8*:47, 1979.
5. Data on file, Medical Department, Sandoz Pharmaceuticals.
6. Kaplan SA, et al: J Pharm Sci *62*:1932, 1973: Mean of 4 patients through 14 days of therapy.

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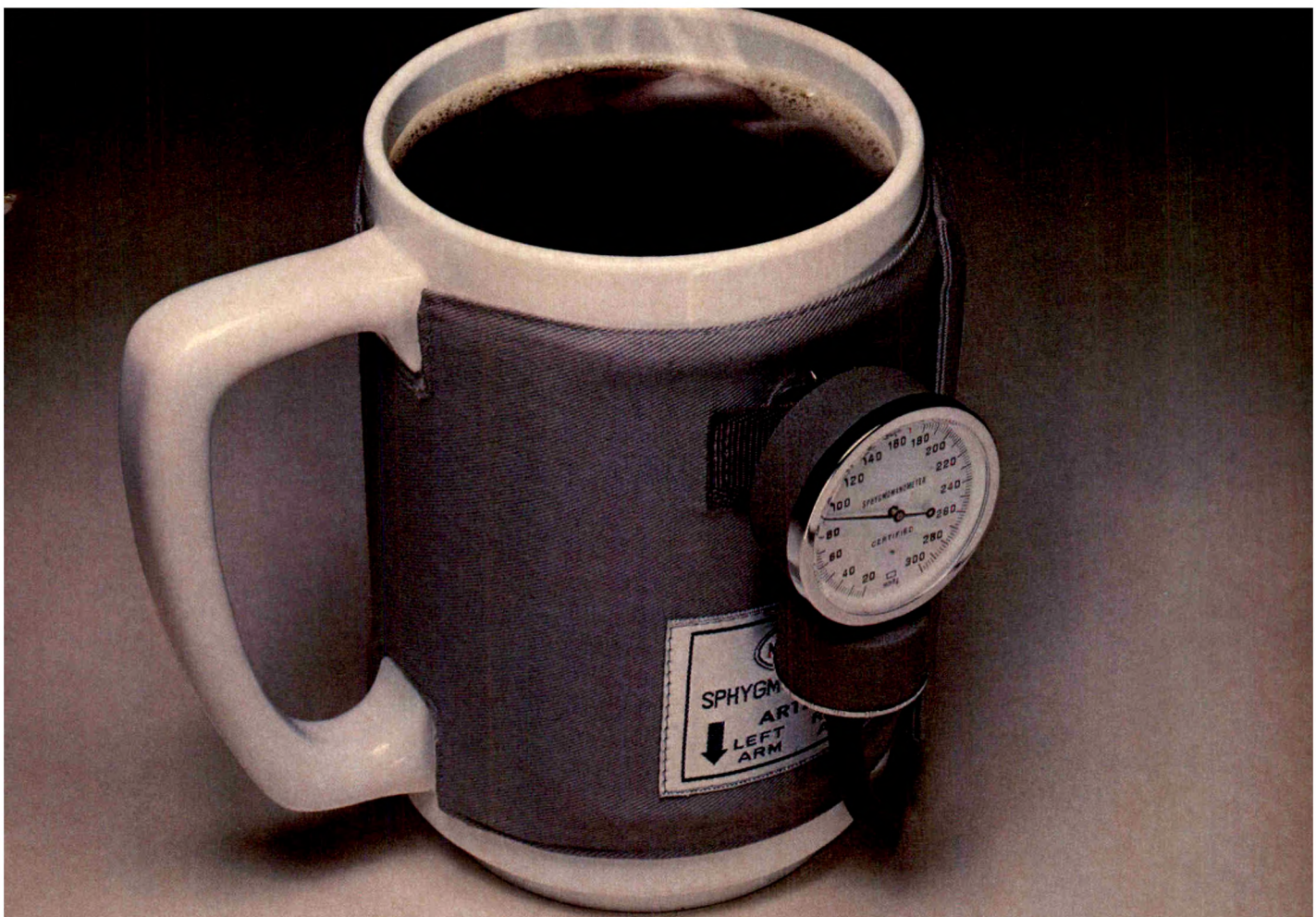

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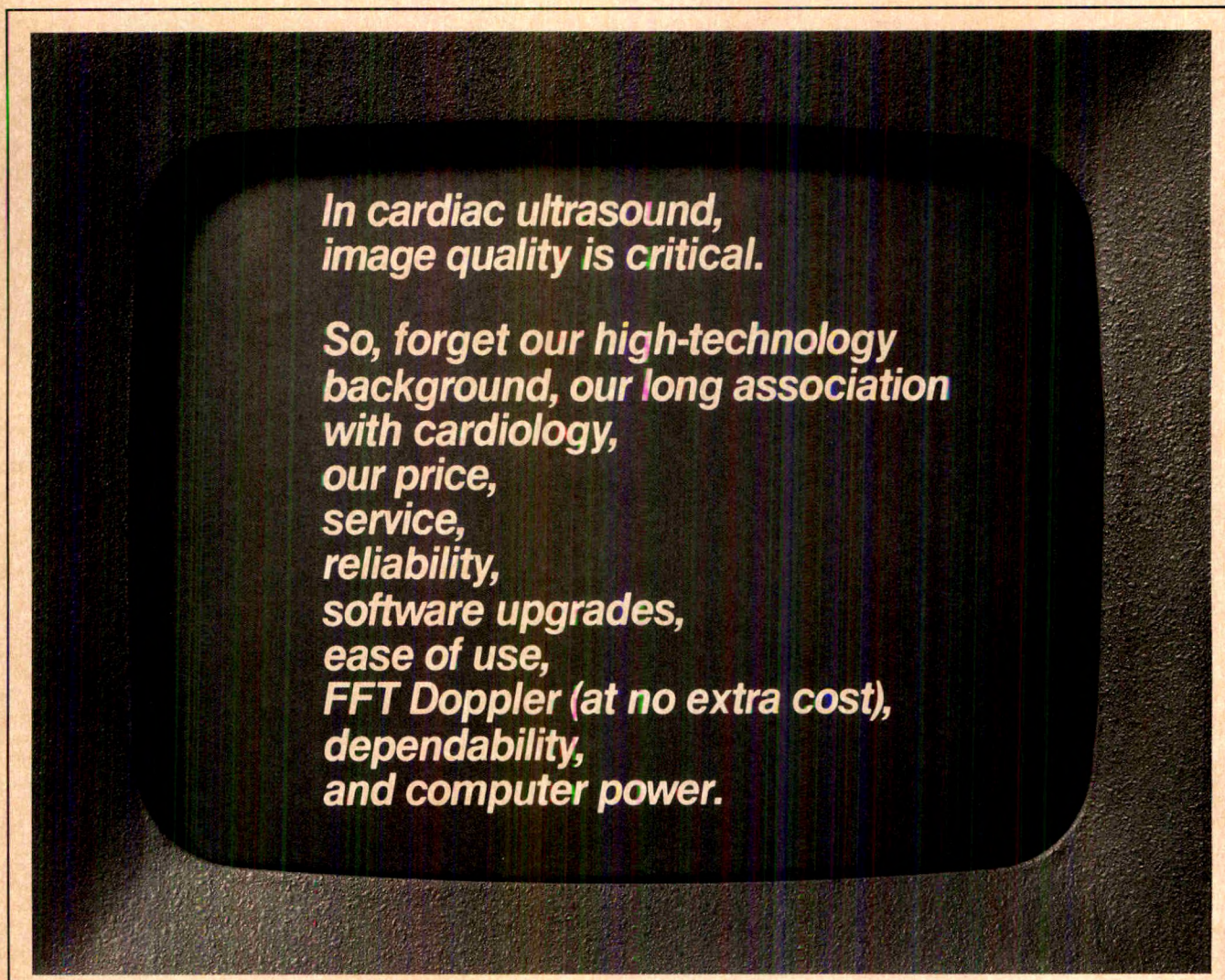

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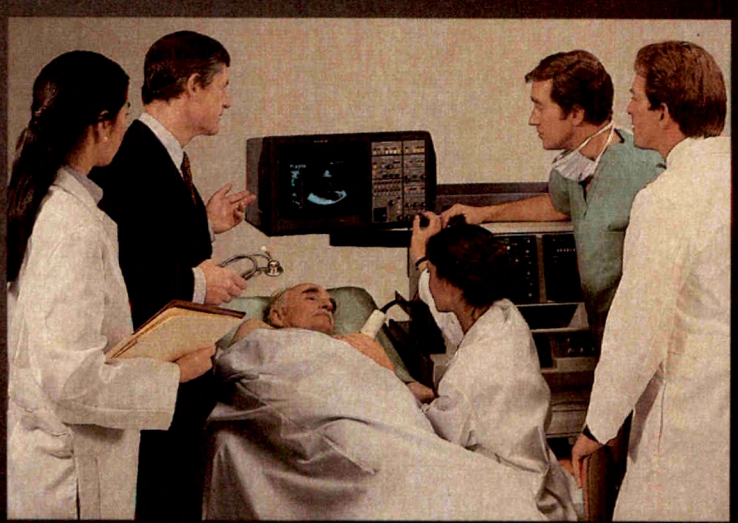

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DRUG INTERACTIONS OF QUINIDINE:

DRUG	EFFECT
With anticholinergic drugs	Additive vagolytic effect.
With cholinergic drugs	Antagonism of cholinergic effects.
With carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decrease excretion of quinidine.
With coumarin anticoagulants	Reduction of clotting factor concentrations.
With tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade.
With phenothiazines and reserpine	Additive cardiac depressive effects.
With hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine.
With digoxin	Increased plasma concentrations of digoxi (see WARNINGS).

PREGNANCY: The use of quinidine in pregnancy should be reserved only for those cases where the benefits outweigh the possible hazards to the patient and fetus. NURSING MOTHERS: Th drug should be used with caution due to excretion of the quinidine in breast milk. ADVERSE REACTIONS: SYMPTOMS OF CINCHONISM (ringing in the ears, nausea, headaches, and/o disturbed vision) may appear in sensitive patients after a single dose of the drug. GASTROINTES TINAL: Diarrhea, nausea, vomiting, abdominal pain. CARDIOVASCULAR: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms (including ventricula tachycardia and fibrillation), paradoxical tachycardia, arterial embolism, and hypotension. HEMA TOLOGIC: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulo cytosis. CNS: Headache, fever, vertigo, apprehension, excitement, confusion, delirium, an syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, nigh blindness, scotomata), optic neuritis. DERMATOLOGIC: Rash, cutaneous flushing with intens pruritus, urticaria. HYPERSENSITIVITY REACTIONS: Angioedema, acute asthmatic episode vascular collapse, respiratory arrest, hepatic toxicity. See package insert for Full Prescribin

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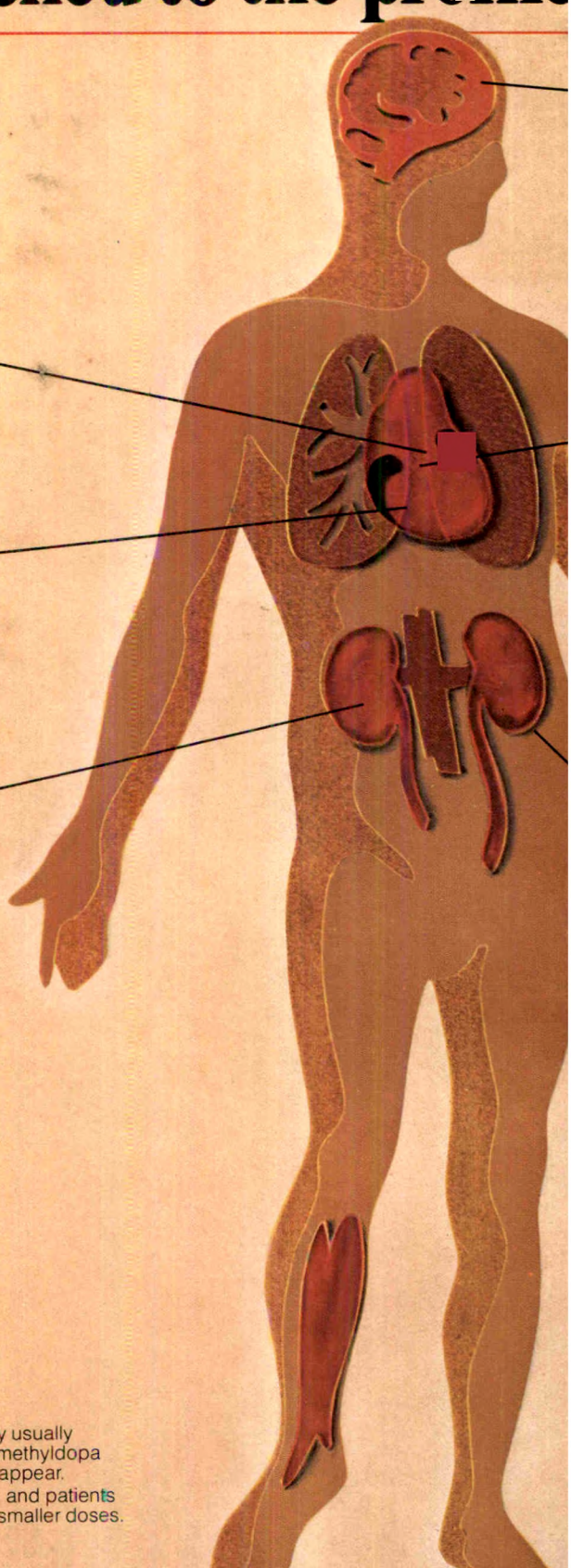
compliance often a problem

ALDOMET provides b.i.d. dosage convenience for many patients.



*Edema (and weight gain) may occur and may usually be relieved by use of a diuretic. Discontinue methyldopa if edema progresses or signs of heart failure appear.

†Methyldopa is largely excreted by the kidney, and patients with impaired renal function may respond to smaller doses.

# of a wide range of older hypertensives

ability to autoregulate cerebral blood flow with postural changes often decreased

With ALDOMET® (Methyldopa, MSD), symptomatic postural hypotension is infrequent. Syncope in older patients may be avoided by lower doses.

cardiac output and heart rate usually normal

ALDOMET has no direct effect on cardiac function, and cardiac output usually is maintained.

total peripheral resistance usually high

ALDOMET lowers blood pressure, apparently by lowering total peripheral resistance.

ongoing therapy usually required

ALDOMET has demonstrated a high degree of efficacy in long-term therapy.

plasma renin activity usually low but may be normal or high

With ALDOMET, normal or elevated plasma renin activity may decrease.

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, or if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed.

Syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease. This may be avoided by lower doses.

MSD
MERCK

ALDOMET® (Methyldopa/MSD)

Tablets, containing 125, 250, or 500 mg methyldopa; Oral Suspension, containing 250 mg methyldopa per 5 ml and alcohol 1%.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions. With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood. At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients. Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, prolonged carotid sinus hypersensitivity, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, colitis, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Bone marrow depression, leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Dermatologic:* Rash as in eczema or lichenoid eruption; toxic epidermal necrolysis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, hyperprolactinemia, amenorrhea, impotence, decreased libido, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, PA 19486

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FROM THE EDITOR

Speeding Up the Manuscript-Reviewing P

All reviewers for the *AJC* are asked to send their reviews to the Editor within 3 weeks. When this time period is met by each reviewer, authors can be notified that their manuscript is accepted or rejected within a month. Although this time sequence operates well for most manuscripts submitted to the *AJC*, some reviewers fail to return their reviews to the Editor for several additional weeks. Indeed, I have been surprised by the length of time some reviewers retain a manuscript before returning it, with or without their opinion, to the Editor.

The "frequent" author is usually a "frequent" reviewer, but the 2 hats are worn at different times. When authors submit manuscripts to a journal, their patience for delay in receiving the "acceptance" or "rejection" decision is generally short; however, when these same authors become reviewers, their patience for delay appears much longer. Reviewers should treat authors as they would like to be treated when they are authors—*this might be the golden rule of reviewing.*

How can a reviewer decrease the length of time between receipt of a manuscript and its return to the Editor? One procedure which has proved useful to me is to *examine the manuscript brief*
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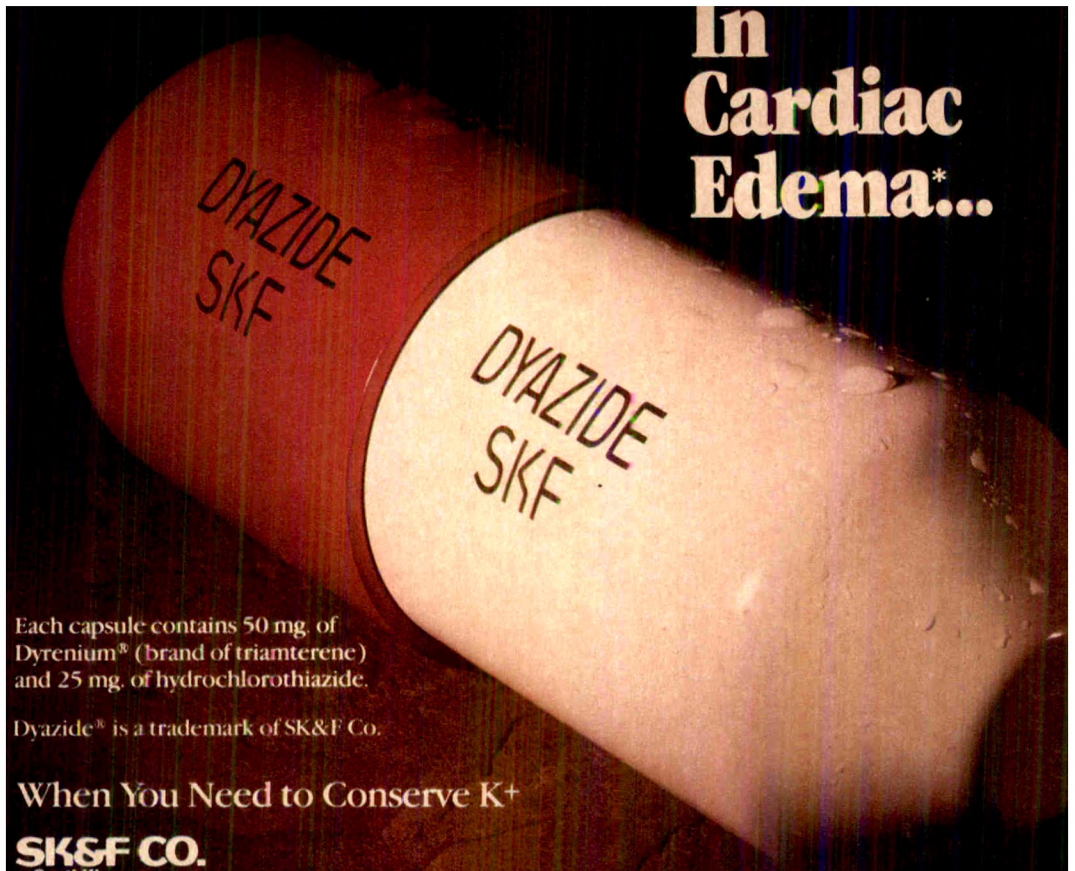

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Dyazide® is a trademark of SK&F Co.

When You Need to Conserve K+

SK&F CO.
a SmithKline company
Carolina, P.R. 00630

Serum K+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

★ **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been recorded. Thiazides have been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, Dyazide should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with Dyazide. The following may occur: transient elevated BUN or creatinine or both; hyperglycemia and glycosuria (diabetic insulin requirements may be altered); hyperuricemia and gout; digitalis intoxication (in hypokalemia); decreasing alkali reserve with possible metabolic acidosis. Dyazide interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and Dyazide should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on Dyazide, although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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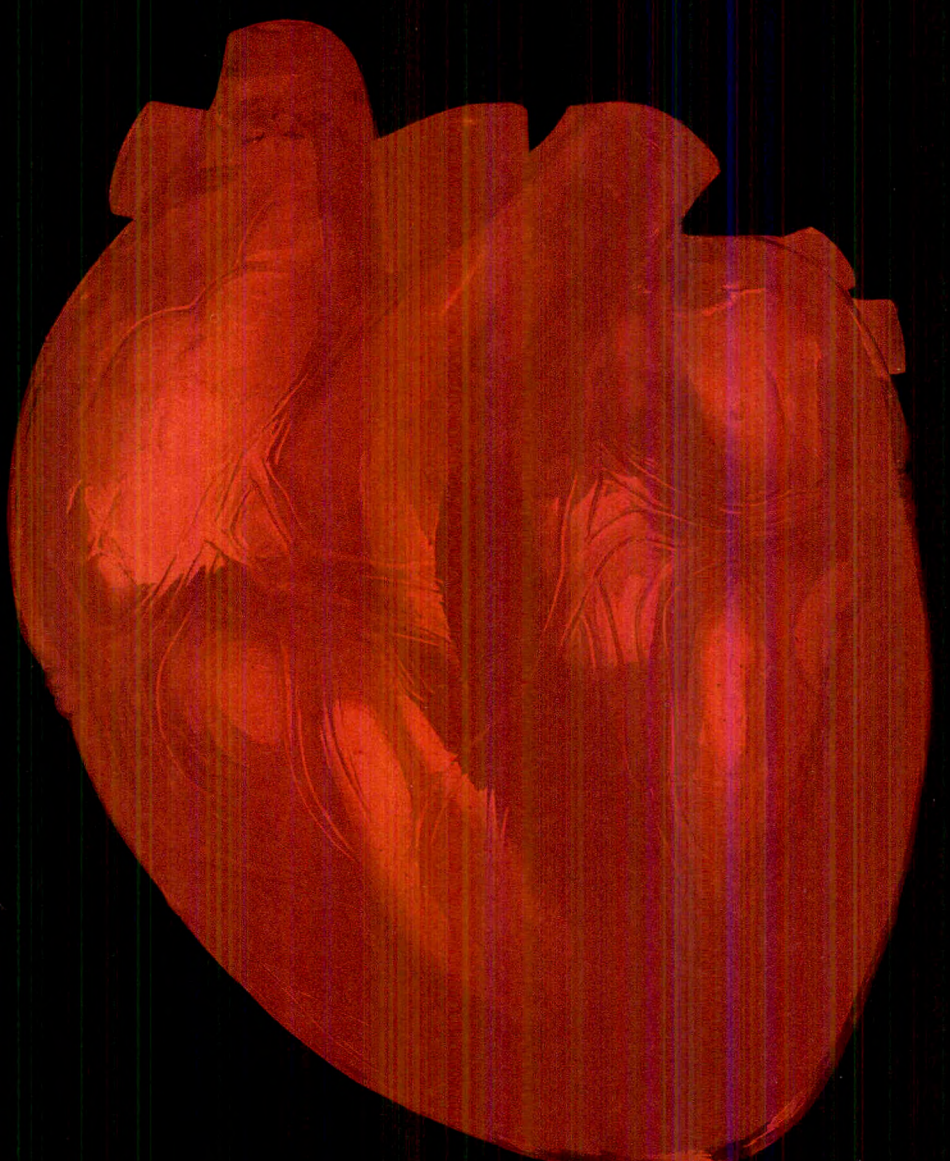

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Versatrax™ Model 7000 Universal A-V Pacemaker

Intended Uses

The Model 7000 universal A-V pulse generator has a wide range of applications in patients requiring permanent cardiac pacing where restoration of A-V synchrony and/or sinus modulated rate variability is indicated to improve cardiac output or to protect against arrhythmias related to the sequence of cardiac impulse propagation. With the Model 7000 programmed in the A-V universal (DDD) mode, such indications may include:

- Some of the sick sinus syndrome conditions such as intermittent sinus bradycardia, sinus arrest or SA block.
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias.
- Atrial and ventricular ectopic arrhythmias.

In the A-V sequential (DVI) mode, the Model 7000 may have application in the following:

- Sick Sinus Syndrome (sinus bradycardia, sinus arrest, SA block, and the brady-tachy syndrome).
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias.
- Atrial and ventricular ectopic arrhythmias.

At any time the Model 7000 can be programmed to the VVI mode in which case the device functions as a ventricular inhibited pulse generator. This mode is intended primarily as a backup mode in situations where it is necessary to disable the atrial circuitry.

Contraindications

General. There are no known contraindications to the use of pacing as a therapeutic modality for control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implantation procedure used by the physician.

DDD Mode. The DDD mode is contraindicated in the presence of atrial fibrillation, atrial flutter and rapid atrial rhythms of slow retrograde conduction.

DVI Mode. In the DVI mode, atrial pacing is ineffective in the presence of chronic atrial fibrillation or flutter.

Warnings

Diathermy. Diathermy should not be used on patients with pacemakers because of possible heating effects in the pulse generator and at the implant site. Electrosurgical units should never be used in the presence of unipolar pulse generators because of the danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead.

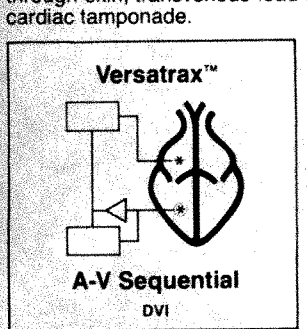
Defibrillation. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. See the specific precautions and warnings in the technical manuals included with the pulse generator.

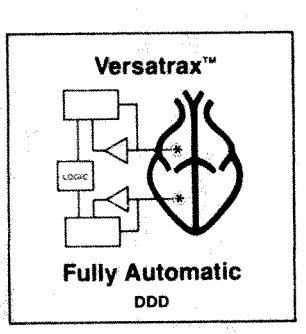
Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.





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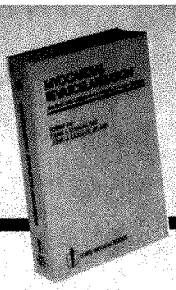

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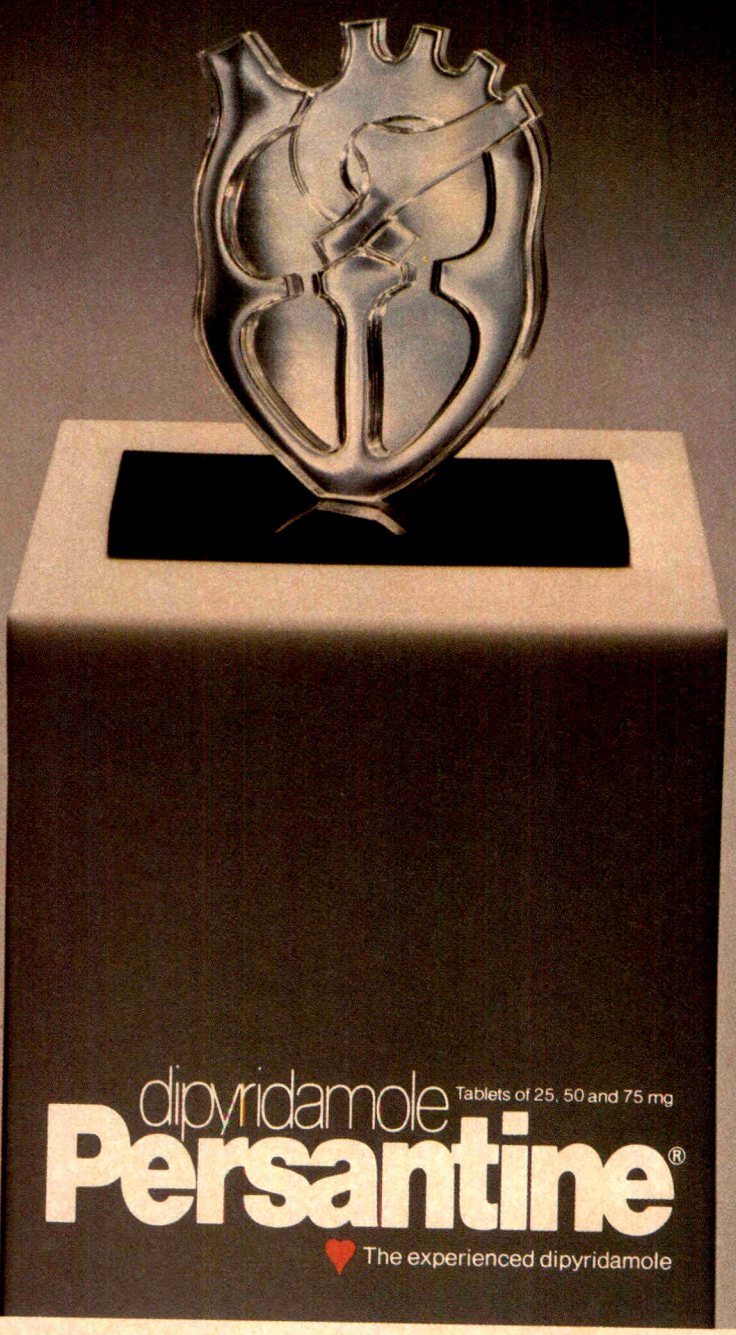

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those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by ssation of undesirable symptoms.
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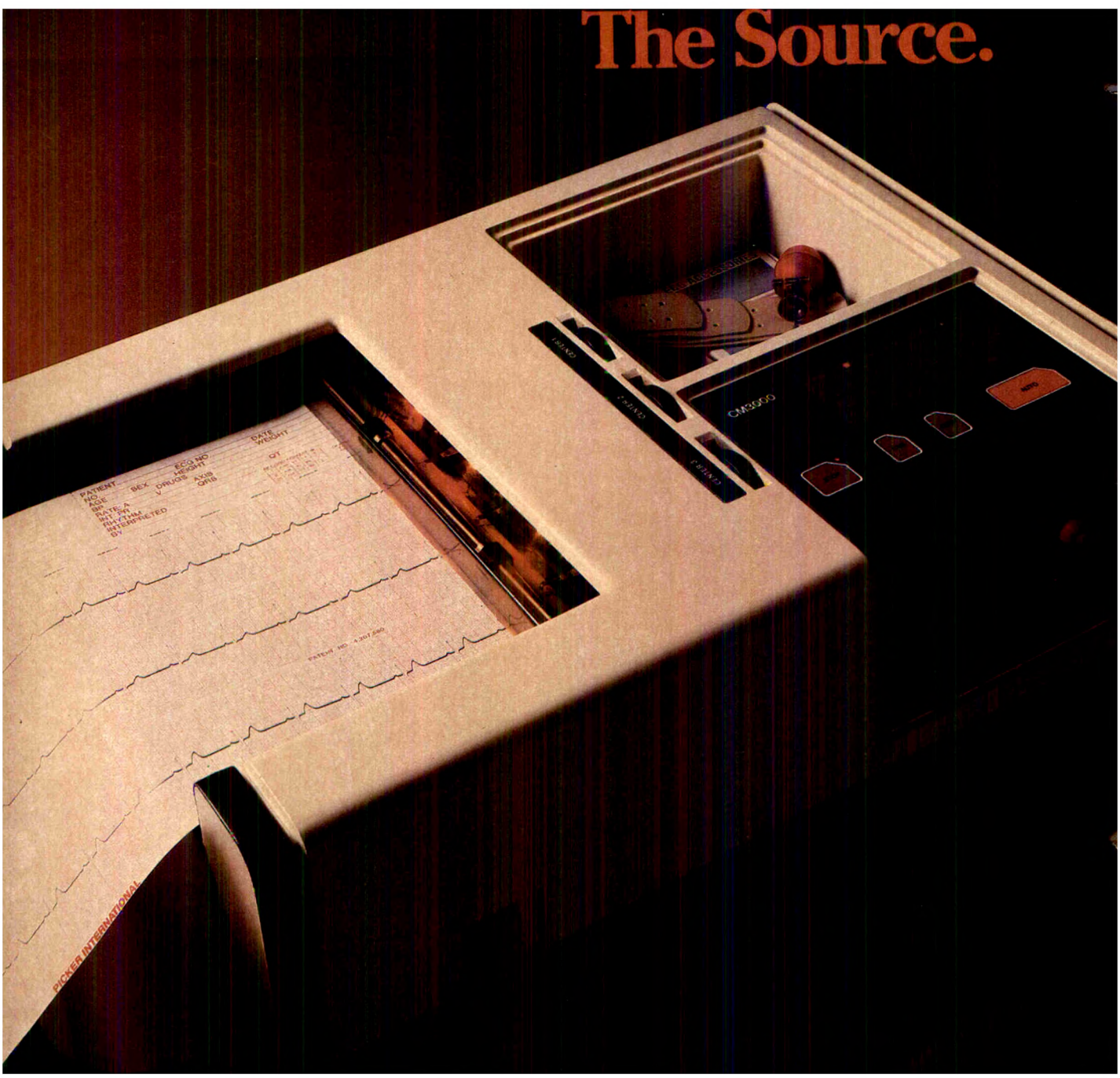
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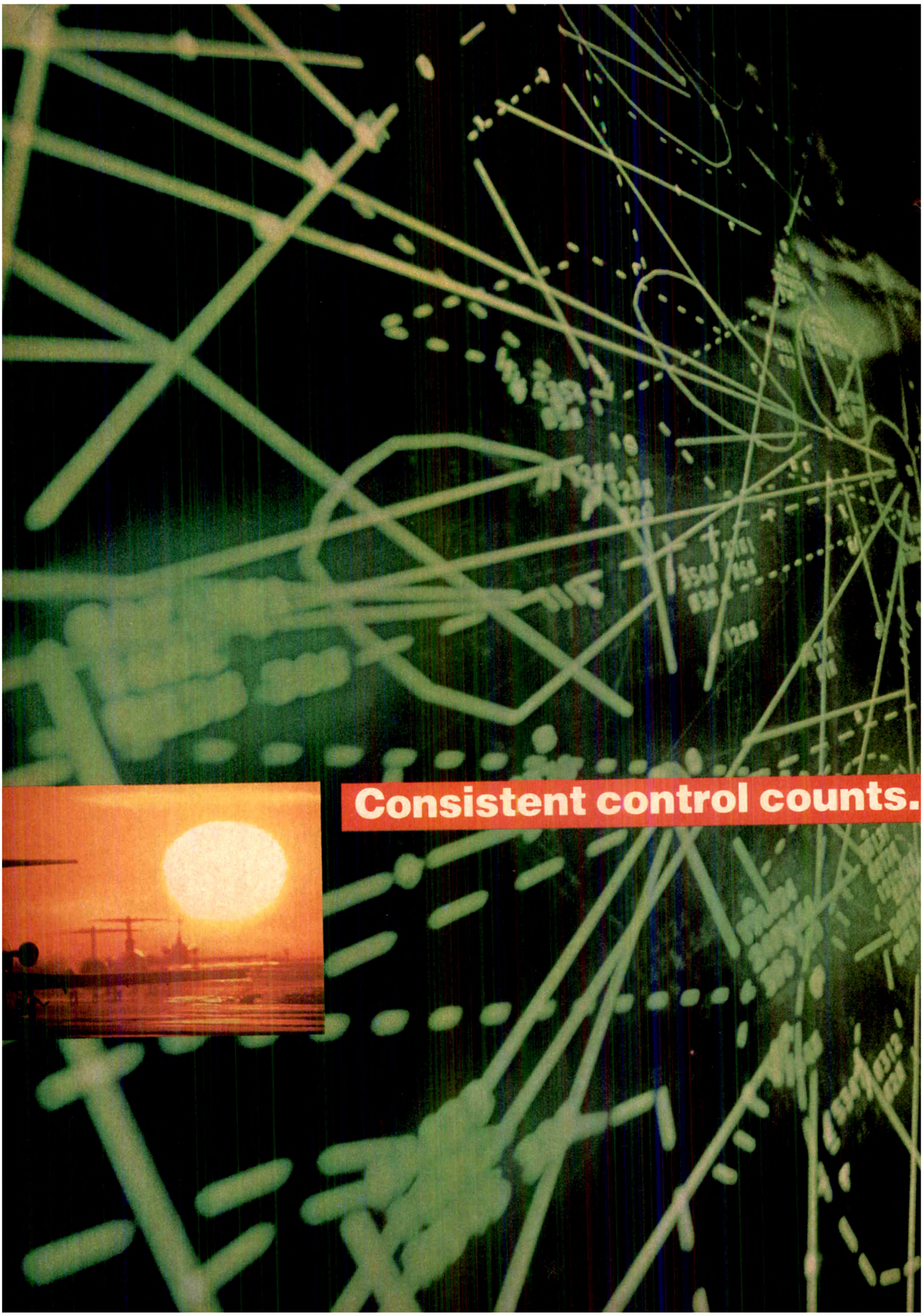
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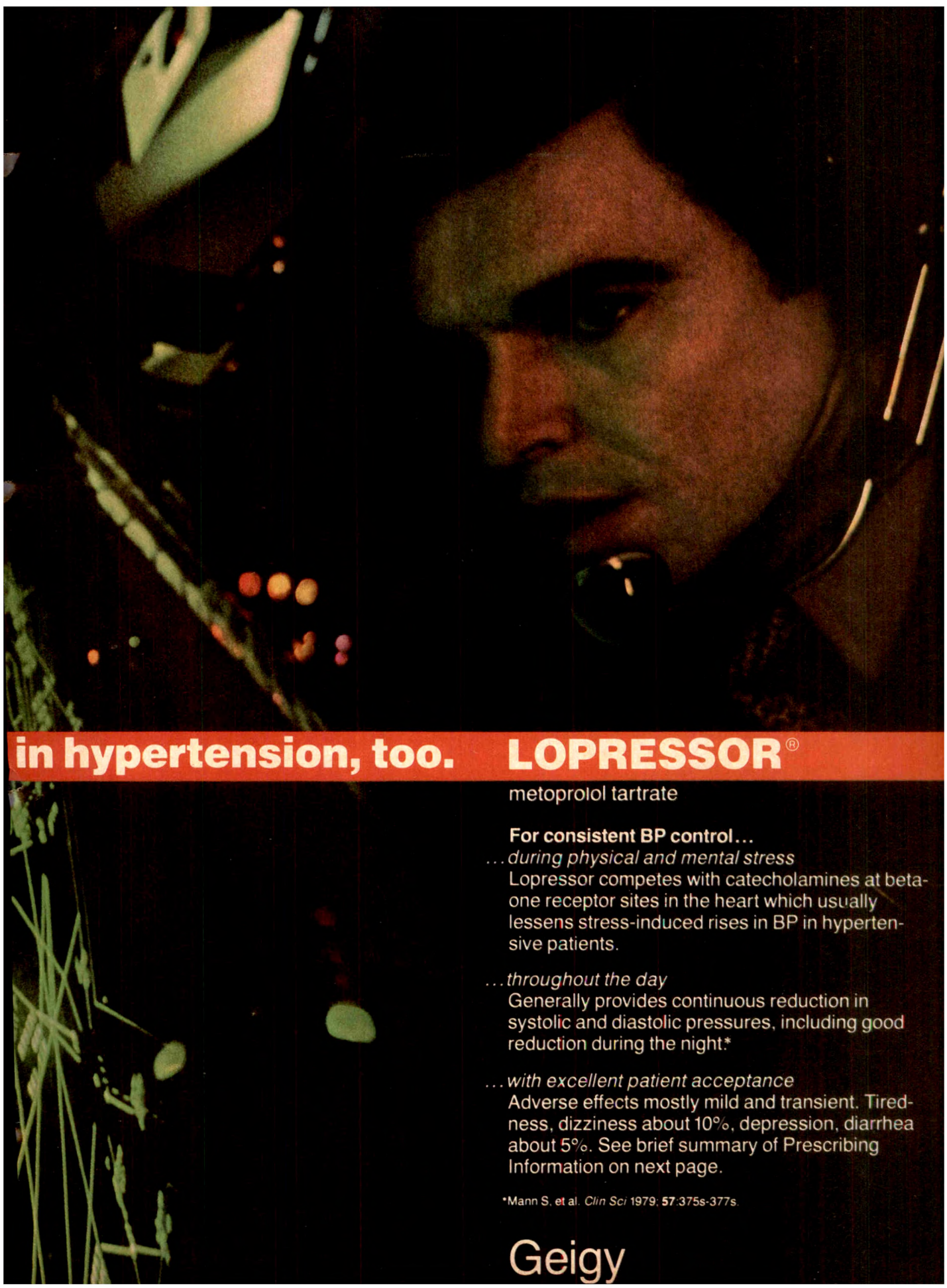

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*Mann S, et al. *Clin Sci* 1979; **57**:375s-377s.

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Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.
Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).
Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.
In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.
Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.
Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**
Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.
Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.
Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.
Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.
Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.
Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.
Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.
Usage in Children: Safety and effectiveness in children have not been established.
Adverse Reactions Most adverse effects have been mild and transient.
Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.
Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**
Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**
Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.
Allergic: Pruritus has occurred in less than 1 of 100 patients.
Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients. The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.
Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.
Cardiovascular: Intensification of AV block (see **Contraindications**).
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.
Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.
Miscellaneous: Reversible alopecia.
Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.
Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta, selectivity diminishes as dosage of Lopressor is increased.
This drug should be stored at controlled room temperature and protected from moisture.
How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.
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NUMBER 6

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CORONARY HEART DISEASE

1199 Effects of Carbon Dioxide, Nd-YAG, and Argon Laser Radiation on Coronary Atheromatous Plaques

GEORGE S. ABELA, SIGURD NORMANN, DONALD COHEN, ROBERT L. FELDMAN, EDWARD A. GEISER, and C. RICHARD CONTI

The use of laser radiation in treatment of obstructive atherosclerotic disease has essentially been unexplored. This work describes the gross and histologic effects of laser radiation on human atherosclerotic plaques using split or intact arteries. Three different lasers (CO_2, Nd-Yag, and Argon) were used under different conditions (dry, immersed in saline or blood). The degree of damage to the atherosclerotic plaque and the underlying vessel wall was evaluated. A direct relation was observed between the energy used (power times duration of exposure) and the depth of penetration into the vessel wall. These preliminary observations suggest that laser radiation can destroy atherosclerotic obstructions and may have potential to recanalize occluded vessels.

1206 Transluminal Laser Catheter Angioplasty

DANIEL S. J. CHOY, SIMON STERTZER, HEIDRUN Z. ROTTERDAM, NIGEL SHARROCK, and IVAN P. KAMINOW

The first transluminal laser angioplasty in animals is reported. An Argon laser and a specialized coronary arterial catheter with a fiberoptic wave guide were used. Immediate histologic changes consisted of a moderate degree of intimal necrosis and some loss of elastic tissue. At 5 days the intima was repaired, but focal elastic tissue loss persisted.

1209 Laser Coronary Angioplasty: Experience With 9 Cadaver Hearts

DANIEL S. J. CHOY, SIMON H. STERTZER, HEIDRUN Z. ROTTERDAM, and MICHAEL S. BRUNO

Laser angioplasty in 16 coronary arteries in cadaver hearts is reported. Argon laser energy is conducted by way of a fiberoptic wave guide in an arterial catheter to the site of obstruction, and thrombi and plaque are vaporized. Successful laser angioplasty was achieved in 8 of 8 artificially thrombosed coronary arteries and in 6 of 7 coronary arteries naturally occluded with calcified plaque.

1212 Prospective Evaluation of Radionuclide Angiocardiography for the Diagnosis of Coronary Artery Disease

ERLE H. AUSTIN, FREDERICK R. COBB, R. EDWARD COLEMAN, and ROBERT H. JONES

The accuracy of rest and exercise radionuclide angiocardiography in the diagnosis of coronary artery disease was examined in this prospective study. Optimal criteria for the presence or absence of coronary disease had previously been derived from a retrospective analysis of 496 patients. In this study these same criteria were applied to 221 consecutive patients presenting with chest pain. Comparison with cardiac catheterization revealed a test sensitivity of 0.87 and a test specificity of 0.54. Thus, the sensitivity of radionuclide angiocardiography compares favorably with other noninvasive techniques for detecting ischemic heart disease. The poor specificity of the test, however, limits its overall accuracy.

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1217 Serial Right Ventricular Thallium-201 Imaging After Exercise: Relation to Anatomy of the Right Coronary Artery

KENNETH A. BROWN, CHARLES A. BOUCHER, ROBERT D. OKADA, H. WILLIAM STRAUSS, KENNETH A. McKUSICK, and GERALD M. POHOST

The relation of right ventricular appearance on exercise thallium-201 images to coronary artery anatomy was examined in 88 patients also undergoing coronary angiography for the evaluation of chest pain. Nonvisualization of right ventricular activity occurred in 10 patients. Nine of the 10 had significant stenosis of the proximal right coronary artery and 7 had high grade stenosis. Normal right ventricular appearance was found in 70 patients, 29 of whom had significant proximal right coronary artery disease. Right ventricular appearance was not affected by the presence or absence of left anterior descending or left circumflex artery disease. Thus, with exercise thallium-201 imaging, right ventricular transient defects suggest high grade proximal right coronary artery stenoses, and nonvisualization of right ventricular activity also suggests significant proximal right coronary disease. However, normal right ventricular appearance occurs frequently despite proximal right coronary artery disease, and does not exclude such disease.

1223 Enhanced Transcardiac l-Norepinephrine Response During Cold Pressor Test in Obstructive Coronary Artery Disease

HILTRUD S. MUELLER, PARINAM S. RAO, PULIPAKA B. RAO, DENNIS J. GORY, J. GERARD MUDD, and STEPHEN M. AYRES

Transcardiac l-norepinephrine responses during cold pressor test in 20 patients with normal coronary arteries were compared with those in 23 patients with abnormal coronary arteries (AC). Baseline hemodynamic data did not differ in the 2 groups, except for left ventricular end-diastolic pressure (mean ± standard deviation, 10 ± 3.7 (NC) and 15 ± 4.5 mm Hg (AC), $p < 0.01$). Baseline l-norepinephrine contents averaged 295 ± 152 (NC) and 250 ± 134 pg/ml (AC) in arterial blood, and 273 ± 152 and 250 ± 115 pg/ml in coronary sinus blood. Hemodynamic responses during cold stimulus were similar in the 2 groups. Also, cold pressor-induced increases in arterial and coronary sinus l-norepinephrine contents were balanced in NC patients, averaging 19 ± 30% and 17 ± 37%. In AC patients, however, a 26 ± 58% increase in arterial l-norepinephrine contents was associated with a 58 ± 62% increase in coronary sinus l-norepinephrine contents ($p < 0.02$), suggesting myocardial net release of l-norepinephrine. It is concluded that transcardiac l-norepinephrine responses during cold stimulus are enhanced in obstructive coronary artery disease.

1229 The QT $>QS_2$ Syndrome: A New Mortality Risk Indicator in Coronary Artery Disease

HARISIOS BOUDOULAS, YOUNG HO SOHN, WILLIAM O'NEILL, ROGER BROWN, and ARNOLD M. WEISSLER

In normal subjects electrical systole (QT) is shorter and closely parallels electromechanical systole (QS_2) throughout the range of resting heart rate. This association of QT to QS_2 prompted the hypothesis that the QT may be more physiologically linked to QS_2 than to heart rate and thus may provide a more potent prognostic indicator than the relation of QT to heart rate. To test this hypothesis 100 patients 14 months after myocardial infarction with an average follow-up of 43 months were studied. There were 20 patients with $QT > QS_2$ and 13 patients with long QT corrected for heart rate (QT_c). There were 20 deaths. The cumulative 5-year survival rate was 35% in patients with $QT > QS_2$ and 91% in patients with $QT \leq QS_2$ ($p < 0.01$); in the same cohort there was no significant difference in 5 year survival in patients with long or normal QT_c (69 versus 82%). Multivariate analysis revealed that the $QT > QS_2$ provides a prognostic indicator independent of the status of left ventricular performance or the extent of coronary artery disease.

Continued on Page A21

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Synopsis of the Symposium

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Calcium antagonists have special usefulness in controlling cases where the myocardial oxygen supply is diminished by coronary vasospasm; their use in combination with nitrates is recommended if Step 2 therapy is unsatisfactory (or if the patient has variant or vasospastic angina).

Consensus of the Symposium

Nitrates are basic in step-care therapy for ischemic heart disease

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Step 2
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Step 3
If still not controlled (or in variant angina): Nitrates + calcium antagonists

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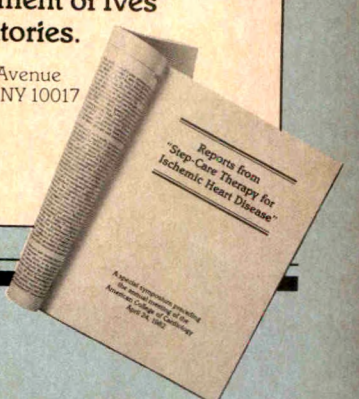

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1236 Transaxial Tomography With Thallium-201 for Detecting Remote Myocardial Infarction. Comparison With Planar Imaging

JAMES L. RITCHIE, DAVID L. WILLIAMS, GEORGE HARP, JOHN L. STRATTON, and JAMES H. CALDWELL

Transaxial tomographic imaging with thallium-201 was compared with standard planar imaging in 38 patients with remote myocardial infarction and 15 nomal patients. The set of transverse-section images was reformatted by 3-dimensional interpolation to obtain tomograms along the long and short axes of the myocardium. Tomographic and planar images were interpreted qualitatively. Overall, tomography detected 87% of previous infarctions while planar imaging detected 63% ($p = 0.01$). The improvement of the tomographic imaging method occurred only in the combined subset of transmural inferior and subendocardial infarctions, and not transmural anterior infarctions. Fourteen of 15 patients without infarction were normal on both planar and tomographic imaging. One normal patient had a defect by both techniques, yielding a specificity of 93% for each. It is concluded that transaxial tomography significantly improves the detection of thallium-201 myocardial perfusion defects in patients with previous myocardial infarction.

1242 Noninvasive Detection of Multivessel Disease After Myocardial Infarction by Exercise Radionuclide Ventriculography

ALAN G. WASSERMAN, RICHARD J. KATZ, PATRICIA CLEARY, VIJAY M. VARMA, RICHARD C. REBA, and ALLAN M. ROSS

Exercise radionuclide ventriculography for the detection of multivessel coronary artery disease was assessed in 74 patients surviving a first myocardial infarction. Of 38 patients with previous inferior infarction, the mean exercise ejection fraction increased from rest ($3 \pm 2.5\%$) in 13 patients with single-vessel disease but decreased ($5.2 \pm 1.4\%$) in 25 patients with multivessel disease ($p < 0.01$). Among 36 patients with previous anterior infarction there was no significant difference in the response to exercise in those with single- and multivessel disease. The sensitivity and specificity of predicting multivessel disease by the criterion of decreasing the exercise ejection fraction by $\geq 5\%$ or the development of a new wall motion abnormality were 80% and 92%, respectively, for patients with inferior infarction but only 69% and 40% for those with anterior infarction. These results suggest that exercise radionuclide ventriculography can discriminate single- and multivessel disease after an inferior but not an anterior myocardial infarction.

1248 Importance of Coronary Risk Factors in the Presence or Absence of Myocardial Ischemia

MARKKU HELIÖVAARA, MARTTI J. KARVONEN, SVEN PUNSAR, and JAASON HAAPAKOSKI

Smoking history, systolic blood pressure, and serum cholesterol concentration were studied for their prediction of 5-year coronary mortality in middleaged and older Finnish men who had initially been classified into 3 groups according to degree of myocardial ischemia: (1) previous myocardial infarction, (2) ischemic heart disease without infarction, and (3) no myocardial ischemia. The risk factors were associated, independently of each other and of age, with the relative risk of coronary death similarly in the 3 groups, whereas their absolute impact on mortality was strongly pronounced among the men with ischemic heart disease, and even more so among those with a previous myocardial infarction. The results suggest that seconday prevention of ischemic heart disease may be important.

1253 Cold Pressor Thallium-201 Myocardial Scintigraphy in the Diagnosis of Coronary Artery Disease

MASOOD AHMAD, JERZY P. DUBIEL, and HELMUT HAIBACH

Thallium-201 myocardial scintigraphy was performed during cold pressor stimulation in 36 patients, 31 with coronary artery disease and 5 with normal coronary angiograms. Transient perfusion deficits were noted in 24 of 31 patients with coronary artery disease (sensitivity 77%), and scintigrams were normal in all 5 patients without coronary artery disease. Exercise electrocardiograms were positive for ischemia in 18 of 24 patients with and in 1 of 5 patients without coronary artery disease (sensitivity 75% and specificity 80%). Exercise thallium-201 scintigrams, obtained in 16 patients, detected all 11 patients with coronary artery disease and were normal in the 5 without such disease. Coronary cineangiograms performed during cold pressor stimulation in 6 patients who had positive cold pressor and exercise thallium-201 scintigrams showed no coronary spasm. The data indicate that cold pressor thallium-201 scintigraphy offers promise as a noninvasive test in the diagnosis of coronary artery disease, especially in patients in whom exercise testing is not feasible.

Continued on Page A24

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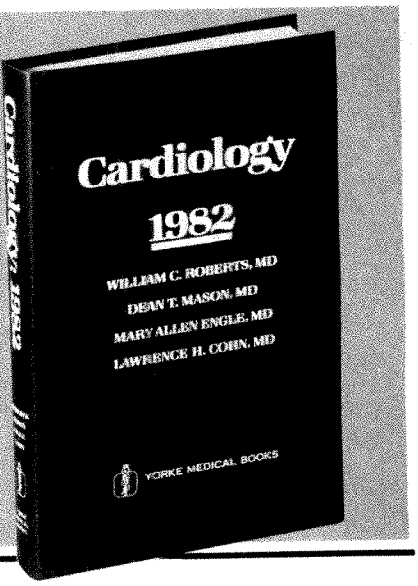

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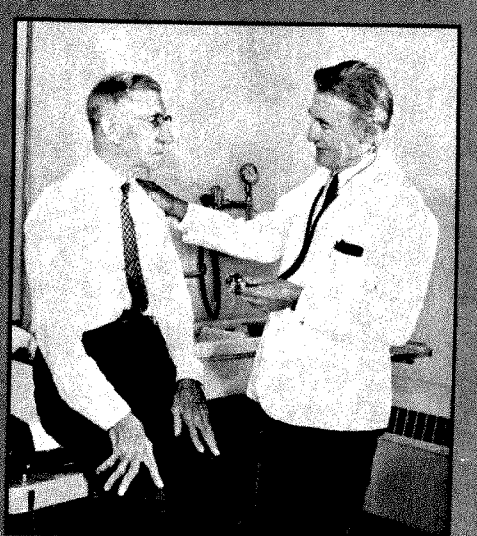

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1258 Plasma Beta-Thromboglobulin as a Measure of Platelet Activity. Effect of Risk Factors and Findings in Ischemic Heart Disease and After Acute Myocardial Infarction

CHARLES W. PUMPHREY and JOAN DAWES

Mean plasma beta-thromboglobulin was found to be increased in 104 patients with ischemic heart disease, compared with that in 101 controls. Smoking, hyperlipidemia, or both risk factors together in otherwise normal individuals were not associated with elevated levels suggesting that risk factors, per se, do not activate platelets. However, the presence of 2 or more risk factors in patients with ischemic heart disease was associated with significantly higher levels than those found in patients with only 1 or no risk factors. This suggests that platelets are activated by the presence of extensive vascular disease. The plasma levels of beta-thromboglobulin in patients with acute myocardial infarction or unstable angina did not change significantly in the days after their admission. Thus the measurement of systemic plasma beta-thromboglobulin indicates the total level of platelet activity in the circulation but is not sufficiently sensitive to provide information about local events.

1262 Use of QRS Scoring and Thallium-201 Scintigraphy to Assess Left Ventricular Function After Myocardial Infarction

NICHOLAS L. DePACE, ABDULMASSIH S. ISKANDRIAN, A-HAMID HAKKI, SALLY A. KANE, and BERNARD L. SEGAL

In this study a statistically significant correlation was found between 3 independent methods for assessing the size of acute myocardial infarction: the QRS score, the size of the resting thallium-201 perfusion defect, and left ventricular ejection fraction. However, in chronic infarction the QRS score was not useful in predicting the ejection fraction; although in these patients a fair correlation was still present between the ejection fraction and the size of the thallium perfusion defect. These data indicate that the size of the defect is related to the ejection fraction in patients with acute or chronic infarction. The QRS score in acute infarction and size of the thallium defect in acute or chronic infarction can categorize patients into those who have low, moderate, and normal ejection fraction.

1269 Current Incidence of Postmyocardial Infarction (Dressler's) Syndrome

EDGAR LICHSTEIN, EDWARD ARSURA, GERALD HOLLANDER, ALVIN GREENGART, and MICHAEL SANDERS

In this study 282 patients with documented acute myocardial infarction were examined. Early postmyocardial infarction pericarditis was seen in 18 patients (6.4%). Information concerning the patient's status was available at 6 months in 229 patients who were discharged alive. There were no documented cases of Dressler's syndrome. We suggest that this decreased incidence or disappearance of Dressler's syndrome is most likely related to decreased use of oral anticoagulants and more aggressive therapy of postmyocardial infarction pericarditis.

1272 Spontaneous Changes in Thallium-201 Myocardial Perfusion Imaging After Myocardial Infarction

ANDREW J. BUDA, JAMES D. DUBBIN, IAN L. MacDONALD, HANS D. STRAUSS, SALLY A. ORR, and HARRY MEINDOK

Changes in regional myocardial perfusion after myocardial infarction have not been investigated extensively. In this study 26 patients underwent exercise thallium-201 myocardial perfusion imaging 3 weeks and 3 months after myocardial infarction. A semiquantitative scoring scheme was used to assess the thallium-201 perfusion scan in 5 regions on each of 3 views. The stress thallium-201 score increased significantly (44.3 $\pm$ 1.2 to 48.3 $\pm$ 1.1, $p < 0.001$) between 3 weeks and 3 months after infarction. The redistribution thallium-201 scores did not change in this same interval. These results indicate that spontaneous improvements in thallium-201 myocardial perfusion imaging may occur in patients after myocardial infarction. This improvement may be related to dynamic changes in coronary perfusion such as spontaneous recanalization or collateral development.

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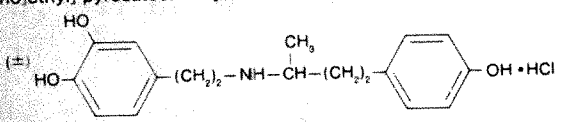

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In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.

Facilitation of atrioventricular conduction has been observed in human electrophysiologic studies and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

Most clinical experience with dobutamine is short-term—up to several hours in duration. In the limited number of patients who were studied for 24, 48, and 72 hours, a persistent increase in cardiac output occurred in some, whereas the output of others returned toward base-line values.

The onset of action of Dobutrex is within one to two minutes; however, as much as ten minutes may be required to obtain the peak effect of a particular infusion rate.

The plasma half-life of dobutamine in humans is two minutes. The principal routes of metabolism are methylation of the catechol and conjugation. In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The 3-O-methyl derivative of dobutamine is inactive.

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine in animals, which indicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

Indications and Usage: Dobutrex is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with Dobutrex.

Contraindication: Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Precautions: 1. During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051, Dobutrex, 250 mg. If the material is not completely dissolved, add another 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstitution time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate 250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

How Supplied: Vials Dobutrex® (dobutamine hydrochloride, Lilly), for Injection (lyophilized), equivalent to 250 mg dobutamine, 20-ml size, rubber-stoppered, in packages of 1. [121979]

Additional information available to the profession on request.

Lilly

200637

Eli Lilly and Company
Indianapolis, Indiana 46285

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CONTENTS

1279 Assessment of the Use of the Age- and Sex-Specific United States Population as a Control Group for Analysis of Survival in Coronary Artery Disease

ROBERT M. CALIFF, KERRY L. LEE, FRANK E. HARRELL, Jr., SUE Y. S. KIMM, SEYMOUR GRUFFERMAN, and ROBERT A. ROSATI

The age- and sex-specific United States population was evaluated as a control group for analysis of the survival of patients with coronary artery disease. The survival of medically treated patients as a group was lower than corresponding age- and sex-specific U.S. population rates. However, the survival of patients with normal left ventricular contraction and stable chest pain was similar to the age- and sex-specific population survival rates. Even after removing deaths due to ischemic heart disease from the general population, the survival of patients with normal coronary arteries exceeded the age- and sex-specific population survival. Due to biases inherent in the selection of patients for cardiac catheterization and the presence of other serious diseases in persons in the general population, the age- and sex-specific U.S. population is not an adequate control group for rigorous analysis of the effect of therapy in coronary artery disease.

MISCELLANEOUS TOPICS

1283 Improved Radiation Protection for Physicians Performing Cardiac Catheterization

EDWARD W. GERTZ, JUDITH A. WISNESKI, ROBERT G. GOULD, and JOHN R. AKIN

This study assesses the potential radiation exposure to physicians performing cardiac catheterization using a Poly C Diagnost System. The radiation exposure to the eyes and thyroid is considerably increased using the left anterior oblique-cranial view compared with the traditional right and left anterior oblique views. To reduce such exposure, a ceiling-suspended shield (60 × 45 cm) was developed. This shield was found effective in significantly reducing (>85%) the physician's radiation exposure in all angulations.

1287 Compression of the Superior Vena Cava and Right Atrium in Cardiac Tamponade

STEPHEN W. MILLER, LAURA FELDMAN, IGOR PALACIOS, ROBERT E. DINSMORE, JOHN B. NEWELL, LINDA GILLAM, and ARTHUR E. WEYMAN

In an attempt to identify specific angiographic patterns that might be useful in distinguishing cardiac tamponade from constrictive pericarditis and other causes of right atrial hypertension, the angiographic and hemodynamic characteristics of 10 patients with cardiac tamponade were compared with similar characteristics in a group of patients with either constrictive pericarditis, effusive-constrictive pericarditis, or pericardial effusion with left ventricular failure. Two predictive angiographic patterns of cardiac tamponade were noted: (1) a tapering or local lateral indentation of the intrapericardial portion of the superior vena cava, and (2) an exaggerated phasic variation in the diameter of the superior vena cava at its junction with the right atrium. Two-dimensional echocardiographic studies in an additional group of 10 patients with cardiac tamponade demonstrated marked concavity of the right atrial free wall corresponding to the angiographic abnormality.

1293 Occlusive Thromboaortopathy (Takayasu's Disease) and Pregnancy. Clinical Course and Management of 33 Pregnancies and Deliveries

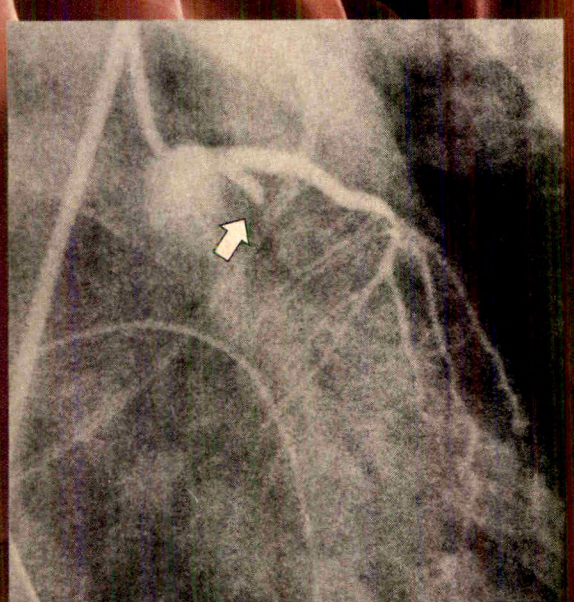
KAICHIRO ISHIKAWA and SHUMPEI MATSUURA

The data presented assist in predicting the outcome of pregnancy and delivery and serve as a guide to the management of patients with occlusive thromboaortopathy, a chronic inflammatory arteriopathy of unknown cause. Although pregnancy did not enhance the inflammatory activity, various cardiovascular events occurred in the perinatal period. During the intrapartum uterine contractions, there was a marked increase in systolic blood pressure in 10 pregnancies of the 22, including 1 pregnancy in a patient who subsequently had a cerebral hemorrhage. There were no maternal or neonatal deaths; however, intrauterine growth of the fetus was retarded when the mothers had severe complications. A prepregnant evaluation of the disease, planning the mode of delivery from both obstetric and nonobstetric indications, and intrapartum and anesthetic considerations, with special reference to the measurement of blood pressure, are important. In addition, reported data on 50 pregnancies in 46 women with Takayasu's disease are reviewed.

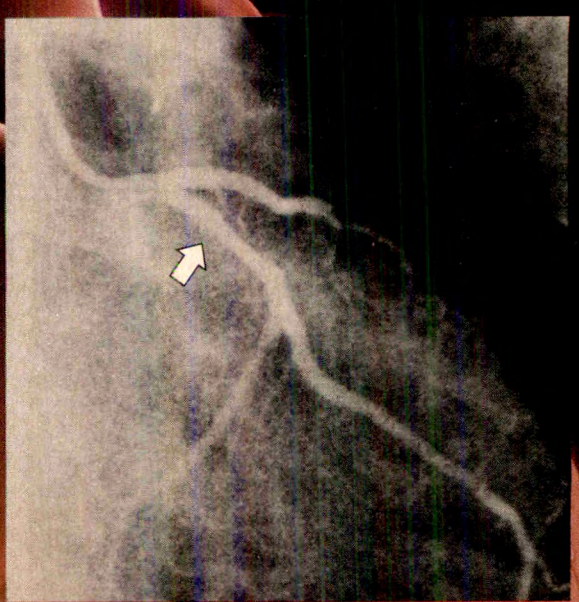
Continued on Page A31

In evolving transmural myocardial infarction

New therapy quickly dissolves acute coronary artery thrombi



Pre-streptokinase
A 38-year-old woman in cardiogenic shock with acute lateral wall myocardial infarction caused by complete left



Post-streptokinase
The left circumflex is now widely patent beyond previous site of obstruction (arrow).

Please see full prescribing information, a summary

STREPTASE®
(streptokinase)

now indicated for acute coronary artery thrombosis.

Streptase® is infused directly into the involved artery during cardiac catheterization.

Efficacy demonstrated in multicenter studies

Coronary artery reperfusion was accomplished in 174 of 221 patients (79%) during evolving transmural myocardial infarction.

Randomized, controlled studies are in progress to determine the effects of reperfusion on salvage of myocardial tissue and reduction of mortality.

Side effects: few and readily controlled

There were no reports of allergic reaction or fever. Seven cases of bleeding at the puncture site and one case of moderate peritoneal bleeding were controlled without terminating therapy. Severe bleeding was reported in only one patient. This patient had a gastric ulcer six months prior to treatment.

Prompt initiation of treatment critical

The greatest benefit is achieved when therapy is initiated within six hours after the onset of symptoms.

Thrombolytic activity and safety record well documented

Streptase® has been effectively used worldwide for nearly a decade. Its record of clinical success is well matched by its record of safety, and both have been extensively reported in the medical literature.

STREPTASE®
(streptokinase)

A major advance in M.I. therapy

Please see full prescribing information, a summary of which appears on the following page.

STREPTASE® (streptokinase)
Brief Summary
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

CORONARY ARTERY THROMBOSIS

Streptase® (streptokinase) has been reported to lyse acute thrombi obstructing coronary arteries, associated with evolving transmural myocardial infarction. Diagnosis of acute myocardial infarction has been confirmed, and the site of coronary thrombosis identified by selective coronary angiography. Other studies have demonstrated that (a) a thrombus is present in approximately 90% of patients evaluated within four hours of onset of symptoms; (b) when compared to concurrent or historical controls, the majority of patients who received intracoronary streptokinase within 6 hours of onset of symptoms showed a more immediate recanalization (within a few minutes vs hours/days) of the involved vessel.

IT HAS NOT BEEN ESTABLISHED THAT INTRACORONARY ADMINISTRATION OF STREPTOKINASE DURING EVOLVING TRANSMURAL MYOCARDIAL INFARCTION RESULTS IN SALVAGE OF MYOCARDIAL TISSUE, NOR THAT IT REDUCES MORTALITY. CONTROLLED STUDIES ADDRESSING THESE PARAMETERS ARE IN PROGRESS AND UNTIL COMPLETED, THOSE PATIENTS WHO MIGHT BENEFIT FROM THIS THERAPY CANNOT BE DEFINED.

CONTRAINDICATIONS

Because thrombolytic therapy increases the risk of bleeding, Streptase® (streptokinase) is contraindicated in the following situations:

- active internal bleeding
- recent (within 2 months) cerebrovascular accident, intracranial or intraspinal surgery (see WARNINGS)
- intracranial neoplasm

WARNINGS

Bleeding

The aim of Streptase® (streptokinase) therapy is the production of sufficient amounts of plasmin for the lysis of intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example, at sites of needle punctures, are also lysed and bleeding from such sites may occur.

Intramuscular injections and nonessential handling of the patient must be avoided during treatment with Streptase® (streptokinase). Venipunctures should be performed carefully and as infrequently as possible.

Should an arterial puncture be necessary during intravenous therapy, upper extremity vessels are preferable. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

When internal bleeding occurs, it may be more difficult to manage than that which occurs with conventional anticoagulant therapy.

In the following conditions the risks of therapy may be increased and should be weighed against the anticipated benefits.

- Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels
- Recent serious gastrointestinal bleeding (within 10 days)
- Recent trauma including cardiopulmonary resuscitation
- Severe, uncontrolled arterial hypertension
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Subacute bacterial endocarditis
- Hemostatic defects including those secondary to severe hepatic or renal disease
- Pregnancy
- Cerebrovascular disease
- Diabetic hemorrhagic retinopathy
- Prior severe allergic reaction to streptokinase
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Should serious spontaneous bleeding (not controllable by local pressure) occur, the infusion of Streptase® (streptokinase) should be terminated immediately and treatment instituted as described under ADVERSE REACTIONS.

Use of Anticoagulants

Concurrent use of anticoagulants with intravenous administration of Streptase® (streptokinase) is not recommended. However, concurrent use of heparin may be required during intracoronary administration of Streptase® (streptokinase). Clinical studies with concurrent use of heparin and lower Streptase® (streptokinase) dosages employed during intracoronary administration have demonstrated no tendency toward increased bleeding that would not be attributable to the procedure or Streptase® (streptokinase) alone. Nevertheless, careful monitoring for excessive bleeding is advised.

Arrhythmias

Rapid lysis of coronary thrombi has been reported occasionally to cause reperfusion atrial or ventricular dysrhythmias requiring immediate treatment. During studies, careful monitoring for arrhythmia was maintained during and immediately following intracoronary administration of Streptase® (streptokinase).

PRECAUTIONS

Use in Pregnancy and Children

Safety and effectiveness of Streptase® (streptokinase) therapy in children and during pregnancy have not been established. Therefore, treatment of such patients is not recommended.

Drug Interactions

The interaction of Streptase® (streptokinase) with other drugs has not been studied. Drugs that alter platelet function should not be used during therapy. Common examples are: aspirin, indomethacin, and phenylbutazone.

Patient Monitoring

Before commencing thrombolytic therapy, it is desirable to obtain a thrombin time (TT), activated partial thromboplastin time (APTT), prothrombin time (PT), hematocrit and platelet count to obtain hemostatic status of the patient.

Intracoronary Artery Infusion

During studies, laboratory monitoring of hemostatic parameters during intracoronary artery infusion showed minimal changes, if any. Heparin was continued during therapy or instituted following therapy and monitored accordingly.

ADVERSE REACTIONS

The following adverse reactions have been frequently associated with intravenous therapy but may also occur with intracoronary artery infusion:

Bleeding

Minor bleeding occurs often with thrombolytic therapy mainly at invaded or disturbed sites. When lytic therapy is continued while local measures are used to control minor bleeding, do **not** reduce the dose as this will increase lytic activity since more plasminogen will be available for conversion to plasmin. Severe internal bleeding involving gastrointestinal, genitourinary, retroperitoneal or intracerebral sites, may occur. Several fatalities due to cerebral and other serious internal hemorrhage have occurred during intravenous thrombolytic therapy.

Should uncontrollable bleeding occur, Streptase® (streptokinase) infusion should be discontinued and, if necessary, blood loss and reversal of the bleeding tendency can be effectively managed with whole blood (fresh blood preferable), packed red blood cells and cryoprecipitate or fresh frozen plasma. Although the use of aminocaproic acid (ACA, AMICAR®) in humans as an antidote for streptokinase has not been documented, it may be considered in an emergency situation.

Allergic Reactions

Reactions attributed to possible anaphylaxis have been observed rarely in patients treated with Streptase® (streptokinase) intravenously. These ranged in severity from minor breathing difficulty to bronchospasm, periorbital swelling or angioneurotic edema. Other milder allergic effects such as urticaria, itching, flushing, nausea, headache and musculoskeletal pain have also been observed.

Mild or moderate reactions may be managed with concomitant antihistamine and/or corticosteroid therapy. Severe allergic reactions require immediate discontinuation of Streptase® (streptokinase), with adrenergics, antihistamines, or corticosteroids administered intravenously as required.

Fever

Although Streptase® (streptokinase) is nonpyrogenic in standard animal tests, approximately one-third of patients treated with Streptase® (streptokinase) intravenously have shown increases in body temperature of ≥ 1.5°F. Symptomatic treatment is usually sufficient to alleviate discomfort. The use of acetaminophen rather than aspirin is recommended.

DOSAGE AND ADMINISTRATION

Lysis of Coronary Artery Thrombi

During clinical studies, Streptase® (streptokinase) was administered selectively into the thrombosed coronary artery via coronary catheter placed by the Judkins or Sones Technique. When administered within 6 hours of onset of symptoms of acute transmural myocardial infarction, at a bolus dose averaging 20,000 IU and a maintenance dose averaging 2,000 IU/min for 60 minutes, greater than 75% of occlusions were opened in less than 1 hour.

How Supplied

Streptase® (streptokinase) is supplied as a lyophilized white powder in 6.5 mL vials (in packages of 10) with color-coded labels corresponding to the amount of purified Streptase® (streptokinase) in each vial as follows:

green — 250,000 IU blue — 750,000 IU

Store unopened vials at controlled room temperature (15-30°C).

Distributed by: **Hoechst-Roussel** Pharmaceuticals Incorporated Somerville, New Jersey 08876 **Hoechst**

Manufactured by: Behringwerke AG U.S. License #97

Q7044-68

CONTENTS

1301 Left Ventricular End-Systolic Stress-Shortening and Stress-Length Relations in Humans. Normal Values and Sensitivity to Inotropic State

KENNETH M. BOROW, LAURENCE H. GREEN, WILLIAM GROSSMAN, and EUGENE BRAUNWALD

The extent of left ventricular fiber shortening is determined by both the wall stress at end-systole and the contractile state. The relations between these variables were assessed in 26 normal subjects using M-mode echocardiography, phonocardiography, and indirect carotid pulse tracings during infusion of methoxamine to alter load and the infusion of dobutamine to increase contractility. End-systolic pressure was estimated from the incisura of a calibrated carotid pulse tracing. Left ventricular end-systolic dimension, wall thickness, and percent dimension change were determined by echocardiography, and end-systolic meridional wall stress was calculated. The relation between end-systolic stress and shortening was inversely linear ($r = -0.83$) and highly sensitive to inotropic state. The relation between end-systolic stress and dimension showed wider scatter ($r = 0.56$) and was less sensitive to changes in left ventricular contractility than was the stress-shortening relation.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1309 Electrophysiologic Testing in the Evaluation of Patients With Syncope of Undetermined Origin

DAVID S. HESS, FRED MORADY, and MELVIN M. SCHEINMAN

Thirty-two patients were evaluated for recurrent syncope with invasive electrophysiologic techniques after conventional neurologic and cardiovascular testing failed to demonstrate a cause. During the electrophysiologic evaluation, 11 patients were found to have laboratory-induced ventricular tachycardia, 5 had evidence of sinus nodal dysfunction, 1 had infra-His atrioventricular block during right atrial pacing, and 1 had quinidine-related ventricular tachycardia. After a mean follow-up of 21.3 ± 1.2 months, 10 of 11 patients with inducible ventricular tachycardia were asymptomatic on laboratory-directed antiarrhythmic therapy, and 5 of the remaining 7 patients with an electrophysiologic abnormality were asymptomatic after pacemaker implantation or alteration of previous drug therapy, or both. During empiric therapy, syncope recurred in 4 of the 14 patients with a normal electrophysiologic study. In patients with syncope of unknown origin, invasive electrophysiologic studies provided a presumptive cause in 56% of patients, with unsuspected ventricular tachycardia accounting for 61% (11 of 18) of the detected abnormalities.

1316 Value of the H-Q Interval in Patients With Bundle Branch Block and the Role of Prophylactic Permanent Pacing

MELVIN M. SCHEINMAN, ROBERT W. PETERS, MARY JANE SAUVÉ, JAWAHAR DESAI, JOSEPH A. ABBOTT, JOHN COGAN, BARRY WOHL, and KATHERINE WILLIAMS

His bundle electrograms were obtained in 313 patients with chronic bundle branch block who were followed up for 3 years. The infranodal conduction time (H-Q interval) was <55 ms in 97 patients (Group I), 55 to 69 ms in 99 patients (Group II), and ≥70 ms in 117 patients (Group III). Mortality and sudden death were similar among groups, but Group III had a greater incidence of progression to high degree atrioventricular block than did Groups I and II. High degree block was found in 4 of 17 patients (24%) with an H-Q interval ≥100 ms. Sixty-two patients underwent permanent prophylactic pacemaker insertion and were compared with 231 who did not. Mortality and the incidence of sudden death were similar among groups, but relief of symptoms was significantly more common in patients with pacemakers. An H-Q interval ≥100 ms identified a group at particularly high risk for high degree block, and prophylactic pacemakers relieved neurologic symptoms but did not prolong life.

1323 Effects of Verapamil on the Electrophysiologic Properties of the Accessory Pathway in Patients With the Wolff-Parkinson-White Syndrome

RICHARD W. HARPER, ERIC WHITFORD, KEN MIDDLEBROOK, JACK FEDERMAN, STAN ANDERSON, and AUBREY PITT

Intravenous verapamil increased the maximal 1:1 atrioventricular conduction through the accessory pathway during incremental high rate atrial pacing in 10 of 12 patients with symptomatic Wolff-Parkinson-White syndrome. The mean increase was 31 beats/min, and the effect of verapamil was most pronounced in patients with

Continued on Page A35

pertaining to the heart.

cardioprotection

the reduction of the and cardiac mortality post-MI patients. See

cardiopulmonary pertaining to the

BLOCADREN is contraindicated in patients with bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see below); cardiogenic shock; and hypersensitivity to this product. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated. In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamine has been observed in patients withdrawn from beta-blocker therapy, exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in

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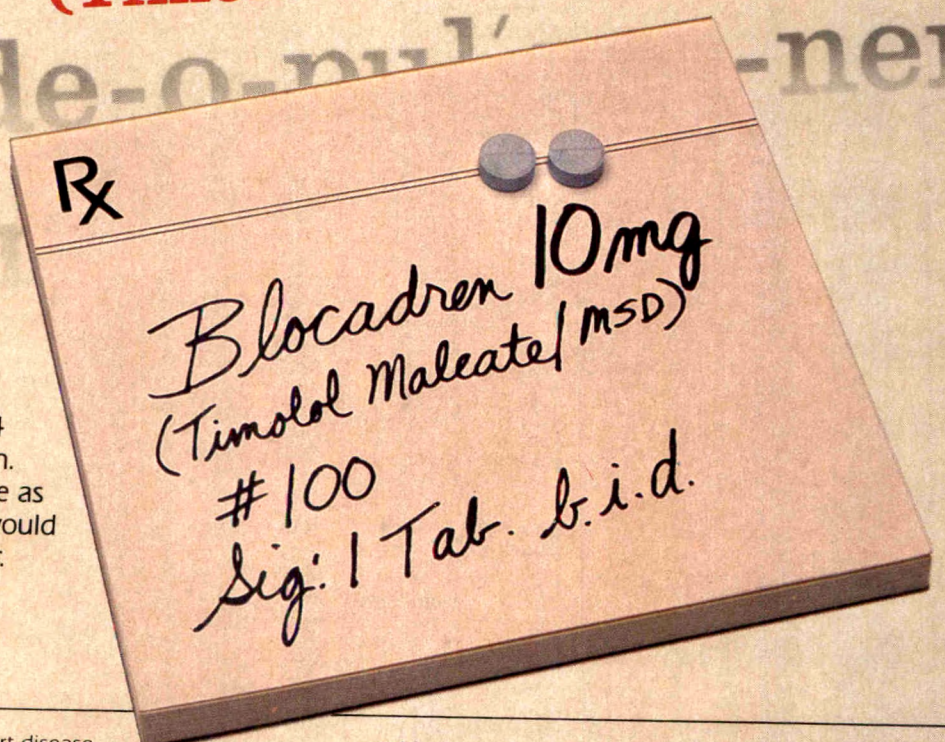
Cardioprotective Blocadren®.
(Timolol Maleate | MSD)

kar"de-o-prə-tec'-shən)
risk of reinfarction for many stabilized

also Blocadren®
(Timolol Maleate|MSD)



Treatment should be initiated within 1 to 4 weeks after infarction. Data are not available as to whether benefit would ensue if initiated later.

patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

MSD
MERCK SHARP & DOHME

For a Brief Summary of Prescribing Information, please see next page of this advertisement.

reduces the risk of reinfarction for many stabilized post-MI patients

BLOCADREN®
(TIMOLOL MALEATE | MSD)

CONTRAINDICATIONS:
Bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to this product.

WARNINGS:
Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In Patients without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS:
General: Impaired Hepatic or Renal Function: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Dosing in the Presence of Marked Renal Failure: Marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20-mg doses. Dosing in such patients should therefore be especially cautious.

Drug Interactions: Close observation of the patient is recommended when BLOCADREN is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

Pregnancy—Category C: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:
BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n = 176) %	Placebo (n = 168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
INTEGUMENTARY		
pruritus	1.1	0
NERVOUS SYSTEM		
dizziness	2.3	1.2
vertigo	0.6	0
paresthesia	0.6	0
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta-blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction†		Withdrawal‡	
	Timolol (n = 945) %	Placebo (n = 939) %	Timolol (n = 945) %	Placebo (n = 939) %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure—Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema—Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

†When an adverse reaction recurred in a patient, it is listed only once.
‡Only principal reason for withdrawal in each patient is listed.

These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole*: extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular*: cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive*: gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Endocrine*: hyperglycemia, hypoglycemia; *Integumentary*: rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal*: arthralgia; *Nervous System*: local weakness; *Psychiatric*: depression, nightmares, somnolence, insomnia, nervousness, diminished concentration; *Respiratory*: cough; *Special Senses*: visual disturbances, dry eyes; *Urogenital*: impotence, urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System*: reversible mental depression progressing to catatonia; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular*: intensification of AV block (see CONTRAINDICATIONS); *Gastrointestinal*: mesenteric arterial thrombosis, ischemic colitis; *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Allergic*: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous*: reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

Clinical Laboratory Test Findings: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations.

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relatively fast control values for this variable. In 4 patients in whom episodes of atrial fibrillation could be compared before and after verapamil, the drug decreased the average R-R interval by a mean value of 45 ms and decreased the shortest R-R interval between preexcited beats by an average of 28 ms. These findings suggest that verapamil may increase the ventricular response through the accessory pathway should spontaneous atrial fibrillation occur in patients with Wolff-Parkinson-White syndrome.

1331 Atrial Excitability and Conduction in Patients With Interatrial Conduction Defects

ROSS J. SIMPSON, Jr., JAMES R. FOSTER, and LEONARD S. GETTES

In order to better understand electrophysiologic characteristics of the atrium in patients with prolonged P-wave durations, atrial excitability and conduction times of 7 patients with P-wave durations <115 ms (Group I) were compared with those in 13 patients with P-wave durations ≥ 115 ms (Group II). In contrast to Group I patients, most patients in Group II had atrial arrhythmias, including sinus nodal dysfunction, atrial fibrillation, or ectopic atrial tachycardia. The electrophysiologic difference between the 2 groups included a higher late diastolic threshold in Group II and a greater increase in intra- and interatrial conduction times of early premature responses in Group II. There was no difference between the 2 groups in refractory periods, shape of the strength interval curve, and conduction times of premature responses occurring late in diastole. These abnormalities of atrial conduction time and excitability may predispose patients with prolonged P waves to atrial tachyarrhythmias.

1338 Termination of Ventricular Tachycardia. Evaluation of a New Pacing Method

MARTIN J. GARDNER, HARVEY L. WAXMAN, ALFRED E. BUXTON, MICHAEL E. CAIN, and MARK E. JOSEPHSON

The efficacy of a combination method of overdrive ventricular pacing plus premature ventricular stimulation to terminate ventricular tachycardia was assessed in 25 patients in whom ventricular extrastimuli and rapid ventricular pacing at comparable cycle lengths and coupling intervals were unsuccessful. The combination method terminated ventricular tachycardia in 6 of 8 patients receiving no drugs in whom extrastimuli or pacing individually were ineffective, and in 6 of 8 patients unresponsive to extrastimuli in whom rapid pacing produced acceleration, and in 9 of 9 patients in whom antiarrhythmic agents made ventricular tachycardia unresponsive to extrastimuli and rapid pacing. The combination method of rapid pacing and extrastimuli appears useful in terminating tachycardias unresponsive to extrastimuli or rapid pacing alone and may avoid acceleration by these methods in certain patients.

1346 Termination of Ventricular Tachycardia: Role of Tachycardia Cycle Length

DENIS ROY, HARVEY L. WAXMAN, ALFRED E. BUXTON, FRANCIS E. MARCHLINSKI, MICHAEL E. CAIN, MARTIN J. GARDNER, and MARK E. JOSEPHSON

The mode of termination of ventricular tachycardia and its relation to tachycardia cycle length was evaluated in 139 patients. Progressively more stimuli were required to terminate tachycardias as the cycle length decreased. Rapid pacing was the most successful method of terminating tachycardia and was the sole method of terminating tachycardias with a cycle length <300 ms. Although procainamide slows tachycardia cycle length, it may have no effect on the ability to terminate, facilitate termination, or make termination of the tachycardia more difficult. Thus, timed extrastimuli are only successful in terminating relatively slow tachycardias, rapid pacing is required for most tachycardias with cycle lengths of less than 300 ms, and procainamide unpredictably affects the ability to terminate tachycardias.

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CONGENITAL HEART DISEASE

1351 Two-Dimensional Echocardiographic Assessment of Dextrocardia: A Segmental Approach

JAMES C. HUHTA, DONALD J. HAGLER, JAMES B. SEWARD, ABDUL J. TAJIK, PAUL R. JULSRUD, and DONALD G. RITTER

A segmental analysis of the atrial-visceral situs connection, ventricular anatomy, and chamber position was utilized for the complete diagnostic assessment in the 2-dimensional echocardiographic examination of 40 patients with the clinical diagnosis of dextrocardia. The echocardiographic findings were confirmed by cardiac catheterization and angiography in 31 cases and at surgery in 26 cases. By use of the location of the liver and drainage of the hepatic veins and inferior vena cava, the atrial-visceral situs was defined in all cases. Pulmonary venous connections were correctly identified in 27 cases. Atrioventricular and ventriculoarterial connections and ventricular anatomy were correctly predicted in 33 cases. Two-dimensional echocardiography allowed the accurate assessment of complex congenital heart defects associated with dextrocardia. Utilizing a segmental approach, one can correctly predict the atrial-visceral situs, ventricular morphology and situs, and atrioventricular and ventriculoarterial connections.

1361 Conotruncal Malformations: Diagnosis in Infancy Using Subxiphoid 2-Dimensional Echocardiography

STEPHEN P. SANDERS, FREDRICK Z. BIERMAN, and ROBERTA G. WILLIAMS

Subxiphoid 2-dimensional echocardiography was prospectively evaluated as a method for diagnosing conotruncal malformations in infants. One hundred four of 109 patients successfully examined were diagnosed correctly, including 46 of 46 patients with d-transposition, 10 of 11 patients with double outlet right ventricle, 34 of 36 patients with tetralogy of Fallot, 8 of 9 patients with tetralogy of Fallot and pulmonary atresia, and 5 of 6 patients with truncus arteriosus communis. Subxiphoid 2-dimensional echocardiography is a sensitive and specific method for diagnosing conotruncal abnormalities in infants.

1368 Two-Dimensional Echocardiographic Assessment of Right Ventricular Volume in Children With Congenital Heart Disease

SATOSHI HIRAISHI, THOMAS G. DiSESSA, JAY M. JARMAKANI, TOSHIO NAKANISHI, JOSEPHINE B. ISABEL-JONES, and WILLIAM F. FRIEDMAN, *With the technical assistance of* BARBARA STERNLIGHT

The ability of 2-dimensional echocardiography to measure right ventricular volume and ejection fraction was assessed in children with congenital heart disease. The area and long-axis length of the right ventricle were obtained from the apical 4-chamber echocardiographic image. The longest length, inflow tract length, and area of the right ventricular sinus were measured from the anteroposterior and lateral planes of the cineangiocardiogram. The echographic long-axis length and area were corrected to the angiographic longest length and area of the sinus. The new corrected echographic longest length and corrected echographic area were applied to 3 area-length formulas to calculate the sinus volume of the right ventricle. Total right ventricular volume was then derived from the sinus volume. All formulas tested predicted right ventricular volumes and ejection fraction well and with equal accuracy.

1376 Two-Dimensional Echocardiographic Evaluation of Persistent Truncus Arteriosus

JOSÉ MARÍN-GARCÍA and INA L. D. TONKIN

M-mode echocardiographic diagnosis of persistent truncus arteriosus is based on the presence of a large arterial trunk overriding the interventricular septum and an inability to image the pulmonary valve. These features, however, do not differentiate this anomaly from cases of tetralogy of Fallot nor from cases with pulmonary valve atresia and ventricular septal defect. Three patients aged 1 to 12 months were studied with a phased-array, wide-angle sector-scanner. Using a combination of short-axis views at the cardiac base and parasternal long-axis views, the truncus arteriosus and the pattern of pulmonary arteries were demonstrated. Type I was found in 2 patients and type II in 1. Examination from the standard planes demonstrated in each case a dilated truncal valve overriding the ventricular septal defect and absence of right ventricular outflow tract. Two-dimensional echocardiography permits accurate diagnosis of persistent truncus arteriosus.

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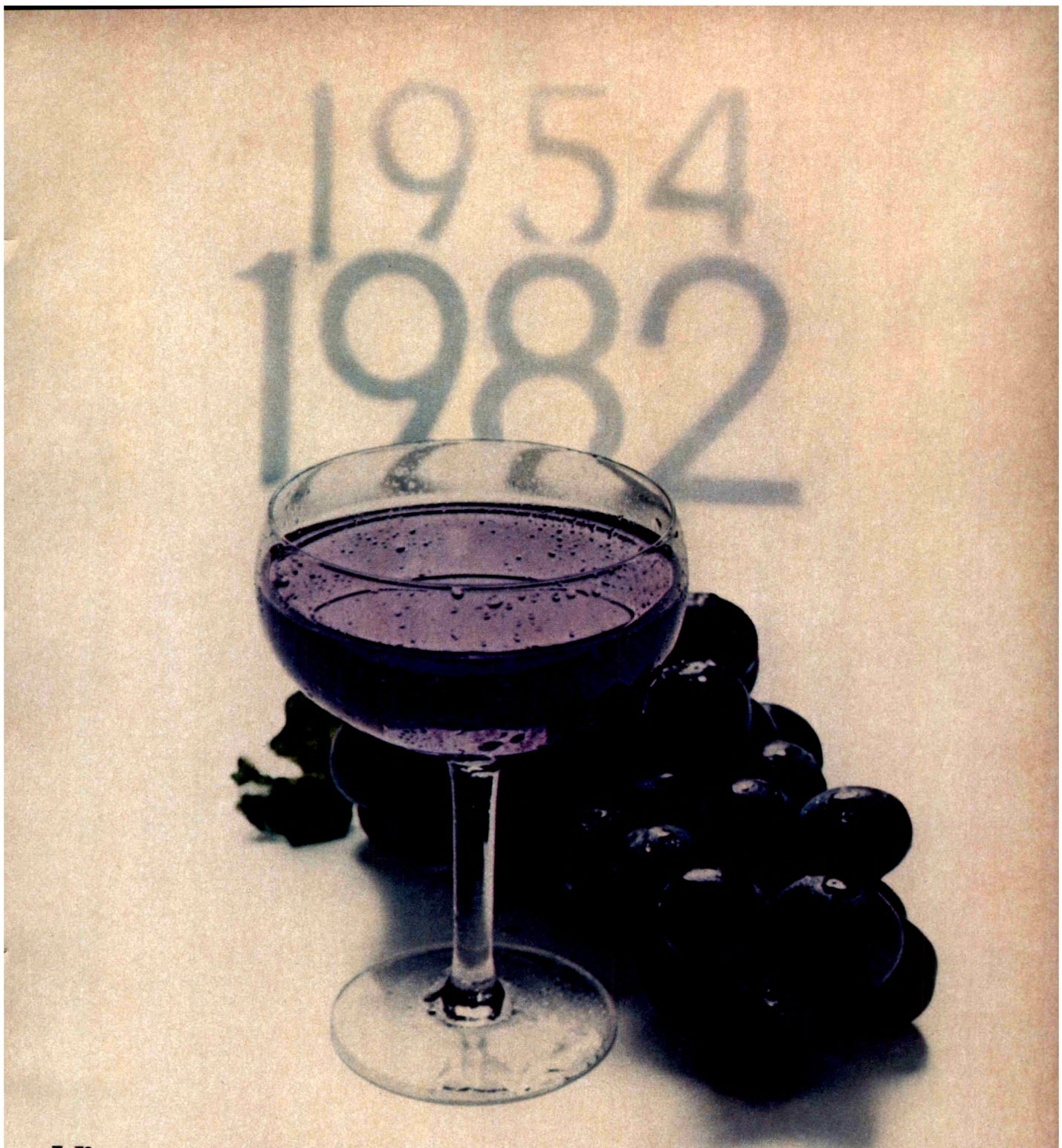

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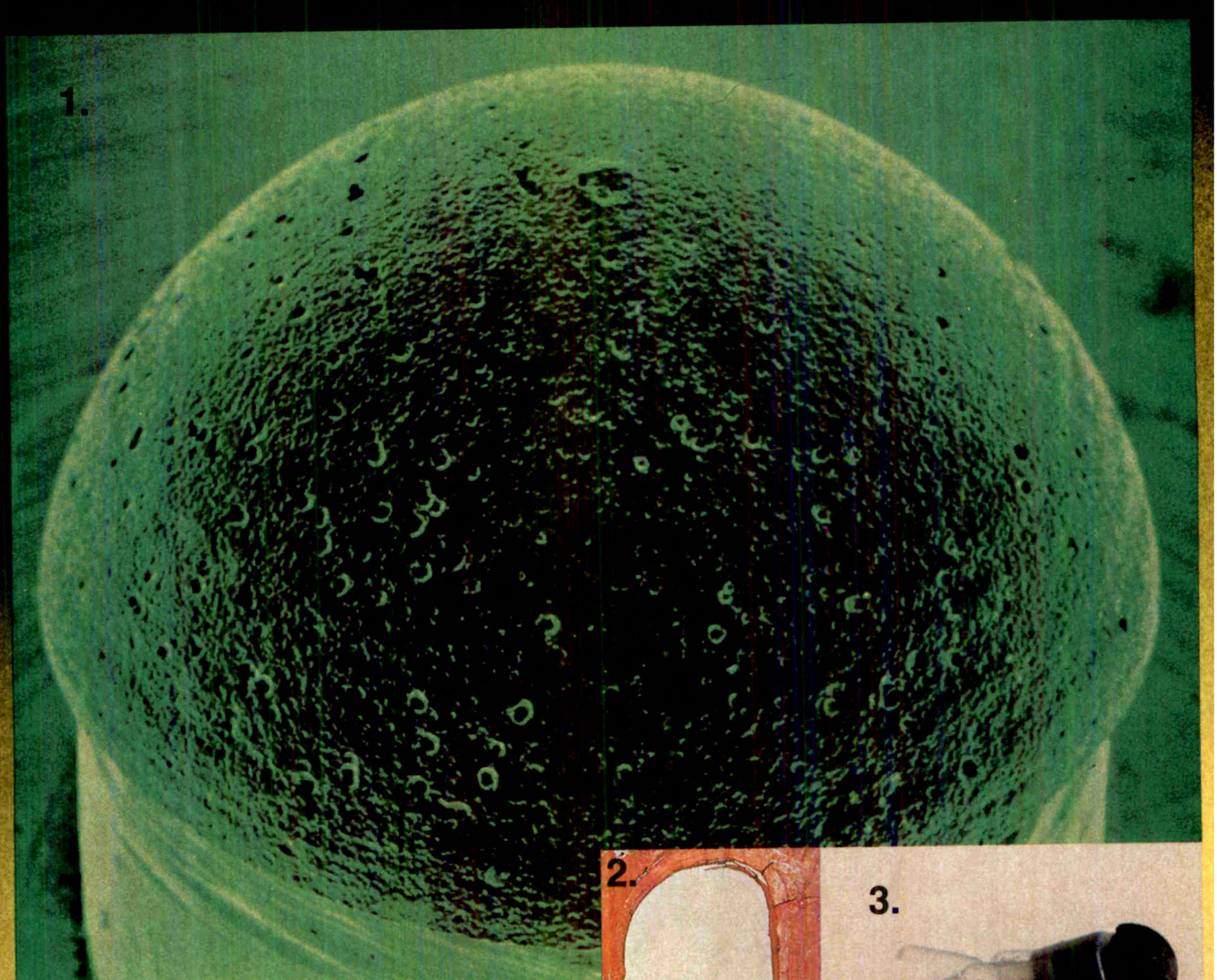

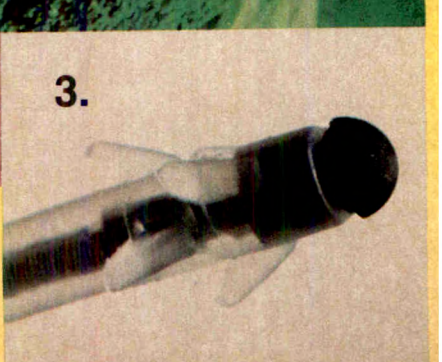

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1380 Two-Dimensional Echocardiographic Prospective Diagnosis of Common Truncus Arteriosus in Infants

THOMAS W. RIGGS and MILTON H. PAUL, *With the technical assistance of* SUE PAJCIC

Two-dimensional echocardiographic prospective diagnosis of truncus arteriosus was made in 7 infants. Two infants had truncus arteriosus type I and 3 had type II, one infant had truncal valve stenosis with an interrupted aortic arch, and 1 had type IV truncus arteriosus with pulmonary hypertension. These images were contrasted with those of an infant with an aorticopulmonary window and intact ventricular septum. Although cardiac catheterization and angiography may be required to assess pulmonary artery pressure, pulmonary vascular resistance, and the distal pulmonary arterial anatomy in truncus arteriosus, 2-dimensional echocardiography can be used to correctly establish the morphologic diagnosis of truncus arteriosus in infants.

1385 Two-Dimensional Echocardiographic Features of Interruption of the Aortic Arch

THOMAS W. RIGGS, TERESA E. BERRY, KALIM U. AZIZ, and MILTON H. PAUL

Two-dimensional echocardiographic features of interruption of the aortic arch are presented based on analysis of the echocardiograms and angiograms from 8 infants. Two infants had type A interruption and 6 had type B. Six infants had a conoventricular septal defect with leftward deviation of the conal septum. The echocardiographic images were compared with those from infants with aortic artesia and hypoplastic ascending aorta or discrete coarctation of the aorta with tubular hypoplasia of the aortic arch. Types A and B were easily discriminated and the caliber of the patent ductus arteriosus was assessed. Subsequent angiography can be more expeditiously performed in this group of critically ill infants.

METHODS

1391 A Simple Teaching Device for Examination of the Arterial and Venous Pulse

ARTHUR KREITENBURG, JOEL S. KARLINER, ROBERT L. ENGLER, and E. ROGER MARCHAND

A simple teaching device for examination of the cervical arterial and venous pulses is described. It is a mechanical device which simultaneously generates a visible jugular venous pulsation and a palpable carotid arterial pulsation to train medical students, physicians, and paramedical personnel. Changing of cams allows the observer to appreciate these pulsations in the normal or a variety of abnormal states. Graphic tracings of wave forms demonstrate the accuracy of reproduction of physiologic tracings. In a test of the device, cardiologists performed significantly better than medical students in the identification of unknown pulsations. The instrument is readily accepted, simple to operate, and fully portable.

1394 Evaluation of Pulmonary and Systemic Blood Flow by 2-Dimensional Doppler Echocardiography Using Fast Fourier Transform Spectral Analysis

STANLEY J. GOLDBERG, DAVID J. SAHN, HUGH D. ALLEN, LILLIAM M. VALDES-CRUZ, HEINZ HOENECKE, and YVONNE CARNAHAN

In this study range-gated Doppler echocardiographic aortic and pulmonary outputs were compared with outputs measured simultaneously by indicator dilution. The results indicate that Doppler-measured aortic flow correlated strongly ($r = +0.94$) with indicator dilution measured output, but Doppler-measured pulmonary flow had a much weaker correlation ($r = +0.72$) with indicator dilution-measured flow. The major difficulty encountered with the Doppler flow technique was echocardiographic determination of great vessel diameter, particularly for the pulmonary artery. If angiographic pulmonary artery diameter was substituted for echocardiographic vessel measurement, the correlation of Doppler and invasive pulmonary flow measurement increased to $r = +0.94$. Other problems encountered with measurement of Doppler flow included encountering turbulence and inability to measure the Doppler beam flow intercept angle simultaneously in 3 axes. Nonetheless, Doppler measurement of aortic and pulmonary flow is clinically practical and accurate if precautions are observed.

Continued on Page A43

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Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions; chronic renal impairment, metabolic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns or adrenal insufficiency. Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Warnings: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and may be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Precautions: *General precautions* – The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. When interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Therefore, the treatment of potassium depletion requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the ECG, and the clinical status of the patient.

Information for patients – To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, patients should be carefully directed to dissolve each dose completely in the stated amount of water.

Laboratory tests – Frequent clinical evaluation of the patient should include ECG and serum potassium determinations.

Drug interactions – The simultaneous administration of potassium supplements and a potassium-sparing diuretic can produce severe hyperkalemia (see Contraindications). Potassium supplements should be used cautiously in patients who are using salt substitutes because most of the latter contain substantial amounts of potassium. Such concomitant use could result in hyperkalemia.

Usage in pregnancy – Pregnancy Category C – Animal reproduction studies have not been conducted with any of the K-Lyte products. It is also not known whether these products can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. They should be given to a pregnant woman only if clearly needed.

Nursing mothers – Many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from oral potassium supplements, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Usage in children – Safety and effectiveness in children have not been established.

Adverse Reactions: The most common adverse reactions to oral potassium supplements are nausea, vomiting, diarrhea and abdominal discomfort. These side effects occur most frequently when the medication is not taken with food or is not diluted properly or dissolved completely.

Hyperkalemia occurs only rarely in patients with normal renal function receiving potassium supplements orally. Signs and symptoms of hyperkalemia are cardiac arrhythmias, mental confusion, unexplained anxiety, numbness or tingling in hands, feet or lips, shortness of breath or difficult breathing, unusual tiredness or weakness and weakness or heaviness of legs (see Contraindications, Warnings and Overdosage).

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1401 The Isovolumic Index: A New Noninvasive Approach to the Assessment of Left Ventricular Function in Man

G. B. JOHN MANCINI, DENNIS COSTELLO, VALMIK BHARGAVA, WILBUR LEW, MARTIN LeWINTER, and JOEL S. KARLINER

In this study, the ability of a new, noninvasive, combined isovolumic index to detect abnormal left ventricular function in human subjects was tested. The isovolumic index was defined as the sum of isovolumic contraction and relaxation times divided by the left ventricular ejection time $\times 100\%$, and was derived from simultaneous electrocardiographic, indirect carotid arterial pulse, and M-mode echocardiographic anterior mitral leaflet recordings. Normal subjects had a value of $24 \pm 7\%$ (standard deviation), in contrast to patients with cardiomyopathy ($65 \pm 14\%$, $p < 0.001$) and a diverse group of patients with coronary artery disease ($40 \pm 15\%$, $p < 0.001$). An abnormal isovolumic index was highly sensitive for identifying patients with coronary artery disease with a reduced ejection fraction or segmental wall motion disorder and was also superior to both abnormal E point-septal separation and the PEP/LVET ratio in detecting abnormal left ventricular function. The isovolumic index is thus a potentially useful and easily obtainable noninvasive marker of left ventricular dysfunction.

EXPERIMENTAL STUDIES

1409 Exercise-Induced Decrease in Flow Through Stenotic Coronary Arteries in the Dog

JEFFREY S. SCHWARTZ, BRUCE TOCKMAN, JAY N. COHN, and ROBERT J. BACHE

In the presence of a coronary stenosis, it is generally believed that exercise-induced ischemia is due to an inadequate increase in coronary blood flow. This study evaluated the hypothesis that exercise may cause a decrease in flow across a severe compliant coronary stenosis. Five unsedated, chronically instrumented dogs were studied. In the presence of a severe circumflex coronary stenosis produced with a snare, exercise caused an increase in heart rate, no significant change in mean aortic pressure, a decrease in pressure distal to the stenosis, an increase in stenosis resistance and a decrease in circumflex blood flow. The decrease in intraluminal pressure distal to the stenosis and thus in the stenosis itself may have resulted in passive narrowing of the stenotic segment, which may have caused the decrease in flow. Exercise, therefore, may produce a decrease in flow through a stenotic coronary artery.

1414 Ventricular Fibrillation Resulting From Ischemia at a Site Remote From Previous Myocardial Infarction. A Conscious Canine Model of Sudden Coronary Death

EUGENE PATTERSON, KURT HOLLAND, BRIAN T. ELLER, and BENEDICT R. LUCCHESI

These studies describe a conscious canine model in which a previous myocardial infarction renders the animal susceptible to the development of ventricular tachycardia in response to programmed electrical stimulation. The subsequent superimposition of regional ischemia at a site remote from the area of previous myocardial injury is accompanied by the development of continuous diastolic electrical activity, ventricular tachycardia, and the sudden onset of ventricular fibrillation. The model affords the opportunity to study electrophysiologic mechanisms leading to the onset of lethal dysrhythmias and to initiate studies aimed at identifying antifibrillatory agents intended for the prevention of sudden coronary death in man.

1424 Quantitative Assessment of Infarct Size Reduction by Coronary Venous Retroperfusion in Baboons

GRAYSON G. GEARY, GREGORY T. SMITH, GLEN T. SUEHIRO, CHARLES ZEMAN, BENJAMIN SIU, and J. JUDSON McNAMARA

The effectiveness of coronary venous retroperfusion to reduce infarct size was evaluated with use of an accurate quantitative method in which infarct size was related to the size of the anatomic perfusion bed of the occluded artery (region at risk for infarction). In an experimental group of 5 baboons, the left anterior descending coronary artery was occluded and coronary venous retroperfusion initiated 1 hour after occlusion. After a 4-hour period of occlusion, retroperfusion was discontinued and anterograde perfusion was simultaneously restored. A control group of 5 baboons underwent an identical procedure without retroperfusion. The perfusion bed of the previously occluded coronary artery was delineated by injection of microvascular dye. The mean percentage of the perfusion bed infarcted was 94.1 ± 0.9 (mean $\pm$ standard error) in the control group and 57.4 ± 3.5 in the retroperfusion group ($p < 0.001$). Hence, retroperfusion initiated after 1 hour of coronary occlusion and maintained for a 4-hour period of occlusion resulted in substantial salvage of ischemic myocardium.

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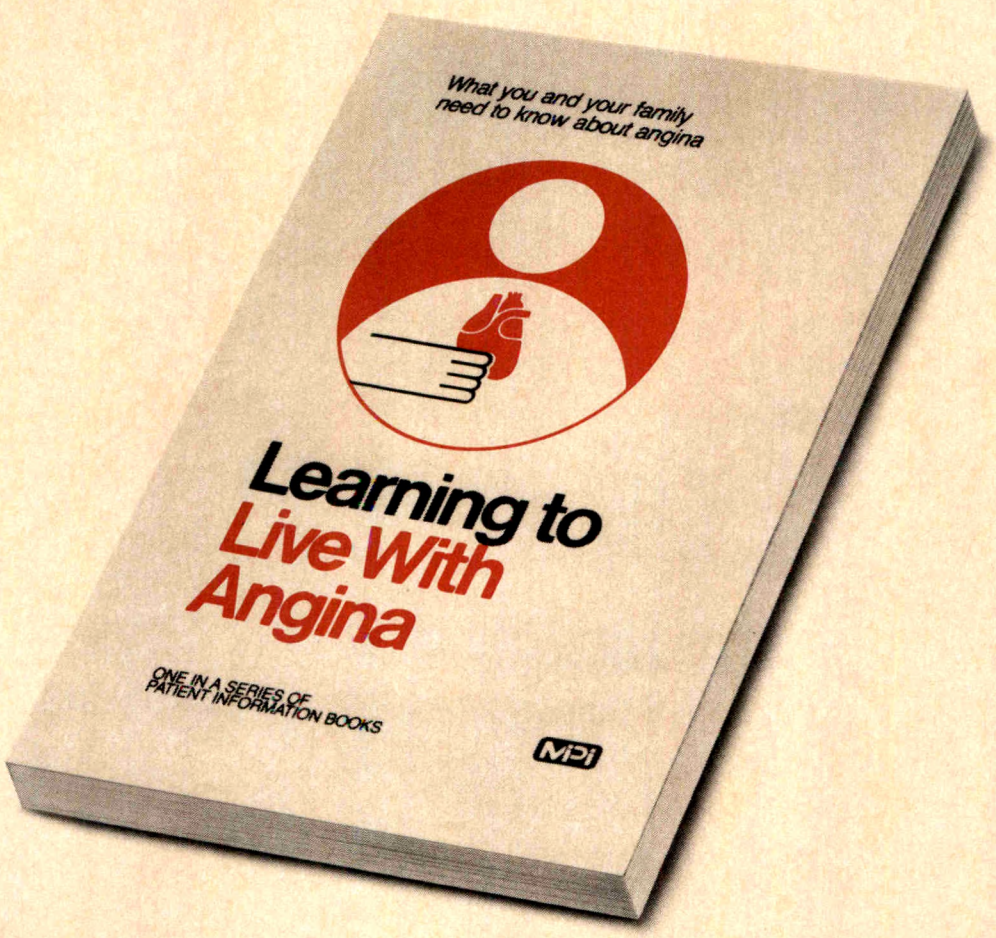

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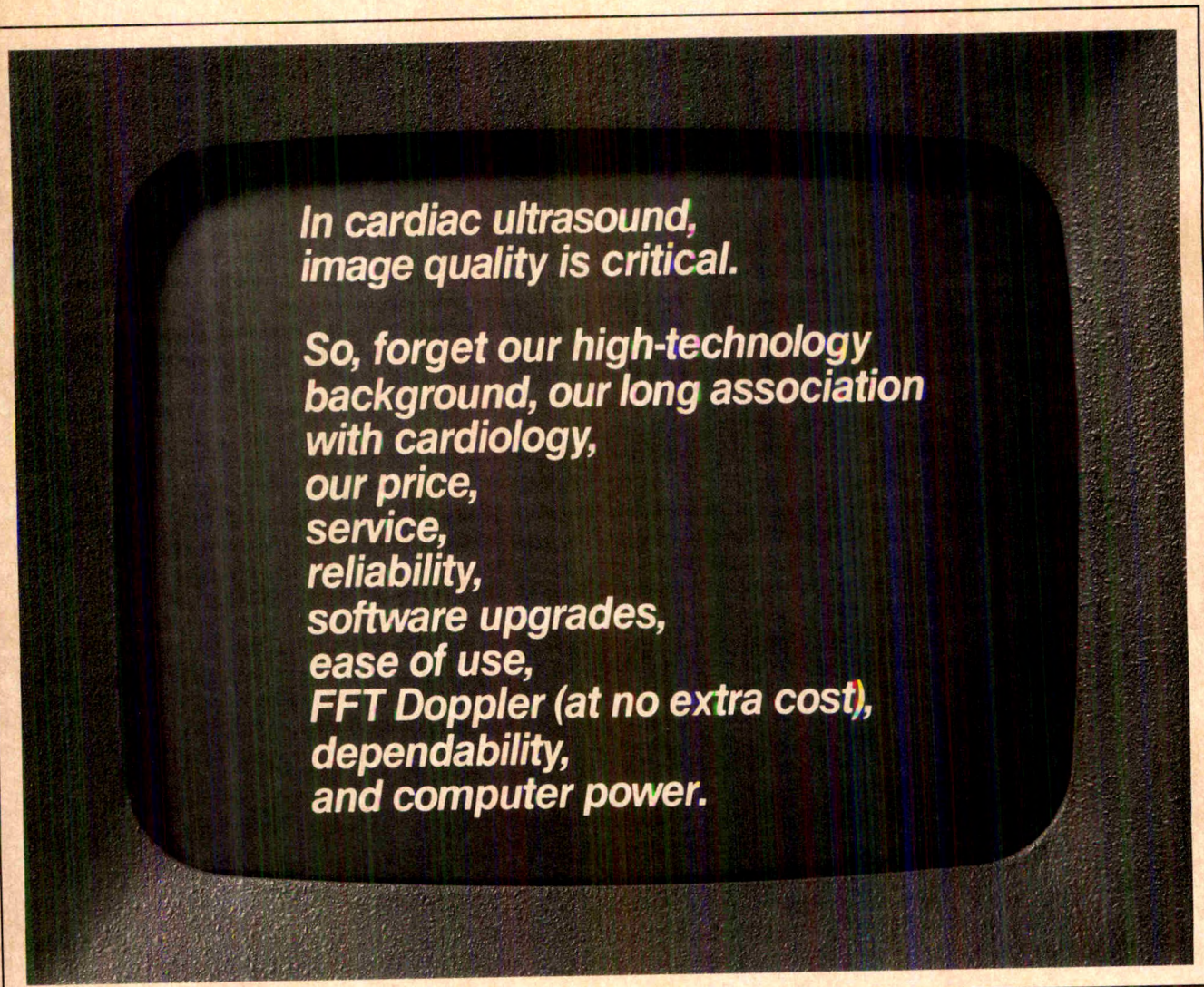

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CORONARY HEART DISEASE

Effects of Carbon Dioxide, Nd-YAG, and Argon Laser Radiation on Coronary Atheromatous Plaques

GEORGE S. ABELA, MD, SIGURD NORMANN, MD, PhD, DONALD COHEN, BS, ROBERT L. FELDMAN, MD, EDWARD A. GEISER, MD, and C. RICHARD CONTI, MD

Laser radiation has been successfully applied in several areas of medical practice. However, its use in cardiology and specifically its effects on obstructive atherosclerosis have largely been unexplored. To evaluate effects of laser radiation on atherosclerotic plaques 25 fresh necropsy atherosclerotic coronary artery segments were exposed to laser radiation with either a carbon dioxide, Nd-YAG, or argon laser. Split or intact segments were prepared under dry conditions or while immersed in saline solution or blood and exposed to laser radiation as power and duration of exposure varied. All 3 lasers were capable of creating controlled injury to atherosclerotic plaques. In general, the magnitude of injury varied according to the total energy delivered (that is, power times duration of exposure). Calcified and noncalcified plaques were penetrated with similar levels of injury. Histologic examination demonstrated that laser radiation produced a wedge incision in the atherosclerotic plaque which was surrounded by zones of thermal and acoustic injury.

Currently, 2 nonsurgical techniques are used to recanalize partly or totally occluded arteries: percutaneous transluminal angioplasty,[1-3] and systemic or regional thrombolytic therapy.[4,5] Laser radiation may offer a third technique to improve perfusion through obstructed arteries.

Laser radiation is a monochromatic and coherent light that can be carried by optical fibers. It has found selected medical uses including destruction of hemangiomas and other cutaneous lesions,[6] hemostasis at the site of bleeding ulcers,[7] and photocoagulation for retinal neovascularization.[8] Recent attempts to anastamose arterial segments with laser radiation have also been successful.[9] Pulmonary stenosis in dogs has partly been relieved using a laser to create holes in the pulmonary valve cusps.[10] Preliminary studies have demonstrated the feasibility of lasers in vitro to damage atheromatous plaques.[11-13] The effects of laser radiation on atherosclerotic plaques, however, have not been extensively described. In this report we describe gross and histologic effects of laser radiation on atherosclerotic plaques under wet (saline solution and blood) and dry conditions using fresh human necropsy coronary arteries.

From the Department of Medicine and Department of Pathology, College of Medicine, University of Florida, Gainesville, Florida. This study was supported in part by the Medical Research Service of the University of Florida, Gainesville, Florida, Biomedical Research Grant 81-116 from the National Institutes of Health, Bethesda, Maryland, and a grant from the Southern Medical Association, Birmingham, Alabama. Dr. Abela is a Merck Fellow of the American College of Cardiology and a Research Fellow of the American Heart Association, Florida Affiliate. Dr. Feldman is the recipient of Research Career Development Award K04-HL00741 from the National Institutes of Health and Dr. Geiser is the recipient of Young Investigator's Research Grant HL-2526 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received and accepted September 23, 1982.

Address for reprints: George S. Abela, MD, University of Florida, Box J-277 JHM Health Center, Gainesville, Florida 32610.

Methods

Human coronary arteries were obtained from 15 patients within 24 hours of death. The coronary arteries were dissected from the heart, partitioned into 2 to 5 cm segments and flushed with normal saline solution to remove blood and loose

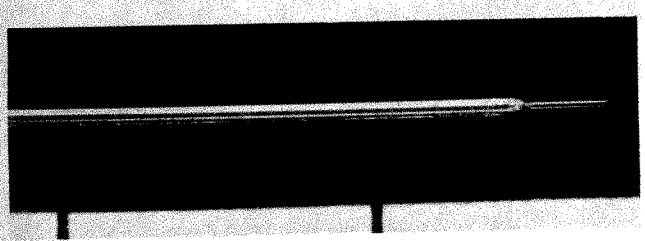

FIGURE 1. Silica fiber used to transmit laser light. The fiber is composed of multiple layers. These are, from inner to outer layer, a silica core surrounded by a silica envelope, a polymer buffer, and finally a Teflon® coating. The distance between the 2 black markers is 1 cm.

debris; 25 segments were selected for study based on atherosclerotic involvement. There were 11 segments of the left anterior descending coronary artery and 7 each from the left circumflex and the right coronary arteries. Experiments were begun within 30 minutes of isolating the coronary artery.

Carbon dioxide laser: Eleven coronary artery segments were split longitudinally, exposing the lumen. Eight split segments were used under dry conditions, and 3 others were placed in a petri dish and immersed in normal saline solution. Atherosclerotic plaques were exposed to carbon dioxide (CO_2) laser radiation (wavelength 10,600 nm) from a Sharplan model 733 laser source (Tel Aviv, Israel). The focal spot size was 0.2 mm. Multiple exposures were made on each coronary artery segment varying the duration of exposure (0.1, 0.2, or 0.5 second) and the amount of power (2, 5, 10, 15, 20, 25, or 30 W).

Nd-YAG and argon lasers: An Nd-YAG (neodymium-yttrium, aluminum, garnet) laser with a wavelength of 1,064 nm (model 510, Control Laser of Orlando, Florida) and Argon laser (model 554A Laser Ionics, Orlando, Florida) with wavelengths of 488 and 514 nm were also evaluated. These lasers were coupled to a fiberoptic system consisting of a 0.5 mm diameter silica fiber (Medicore Optical Fiber Med 200, Quartz Products, Plainfield, New Jersey), which was polished smooth at both ends and 80 to 100 cm long (Fig. 1). One end was aligned with the focused laser beam as it exited from the laser, and the free end was used for lasing. The power reading on the laser meter did not represent the actual power delivered at the fiber tip because of attenuation over the length of the silica fiber. To measure the actual power at the fiber tip, a power meter (Coherent model 105 Power Meter, Palo Alto, California) was positioned adjacent to the tip of the free end of the fiber and the power range of each laser examined. Only the power measured at the tip will be reported.

Seven intact coronary artery segments, chosen because of multiple areas of totally occlusive atherosclerosis, were used to evaluate effects of Nd-YAG laser radiation during immersion in normal saline solution. The occluded portion of the segments ranged from 5 to 10 mm long. In 2 segments 6 separate regions were lased after staining with cardiogreen or Sudan black. Before lasing, excess dye was removed by washing the segments in saline solution. Under the direct vision, the free end of the optical fiber was placed in line with the coronary artery lumen and against the atherosclerotic plaque. It was necessary for the fiber tip to be touching the plaque as the power density (W/cm^2) delivered decreased markedly as distance from the tip increased beyond 1 mm. The power at the tip was varied between 1.2 and 9 W. The laser was used in continuous wave mode. Every 5 to 10 seconds the magnitude of plaque injury was visually assessed, the laser position was adjusted if necessary, and lasing was continued until the plaque was penetrated or the artery perforated. In many experiments, several new lumens were lased in an occluded coronary artery segment. The effect of the Nd-YAG laser also was evaluated in a similar fashion in 5 intact arterial segments immersed in citrated whole blood. The Argon laser was tested in a similar fashion as the Nd-YAG laser. Two arterial segments were used, 1 immersed in saline solution and the other in blood.

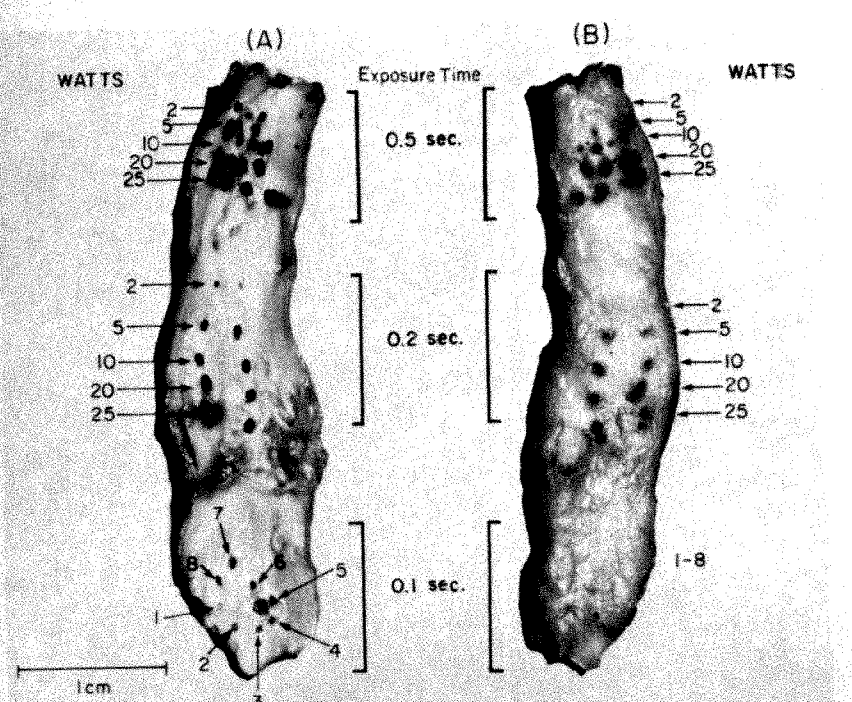

FIGURE 2. Example of increasing plaque damage from a split coronary artery segment as the total energy of exposure was increased (CO_2 laser under dry conditions). Multiple exposures were made at progressively higher power (watts) and longer duration (seconds). **A,** the lumen side of an anterior descending artery. As total energy increased first crater depth and diameter increased and then perforation occurred. **B,** the serosal side of the same artery showing perforation with increased energy.

Histology: After exposure to laser radiation, all tissue samples were fixed in 10% neutral buffered formalin and embedded in paraffin. Tissue blocks were cut in sections of 4 μm thickness. Sections from each tissue block were stained with hematoxylin and eosin. Ten sections were stained with either Masson's trichrome or with Verhoff-Van Gieson's stain. Each section was evaluated by light microscopy at a range of magnifications from 25 to 120×.

Calculations and definitions: In intact occluded coronary artery segments lasing was considered successful if the plaque was penetrated and a new lumen established. Perforation was defined as rupture through the entire thickness of the arterial wall. Total energy delivered in joules was calculated as the product of amount of power (watts) and duration of exposure (seconds).

Results

Effects of exposure to carbon dioxide laser radiation under dry conditions: Over 100 applications of carbon dioxide laser radiation were made under dry conditions; an example of 1 segment is shown in Figure 2. Increasing duration of exposure at a constant power produced an injury similar to that of increasing power at a constant duration of exposure. When total energy was 1 to 2 J, the plaque was penetrated. Between 2.5 and 5 J, both the plaque and the media were penetrated. With exposure >7.5 J, the vessel was consistently perforated.

Histologic examination was done in 108 sections. As observed by inspection of the gross specimen, crater diameter and depth were directly related to total energy applied. Three zones of tissue injury in the atheroma and surrounding vessel wall were observed (Fig. 3 to 5). Zone 1 consisted of a crater that was the result of tissue vaporization. The vaporization of tissue was complete, as no debris remained. Zone 2 consisted of a region of thermal-induced necrosis and coagulation. It consisted of a narrow band of tissue charring and then a region of tissue coagulation that varied between 5 and 15 μm in diameter. Zone 3 comprised a distal and diffuse region of acoustic or shock injury. This region could extend up to 30 μm from the edge of zone 1. It gradually faded into

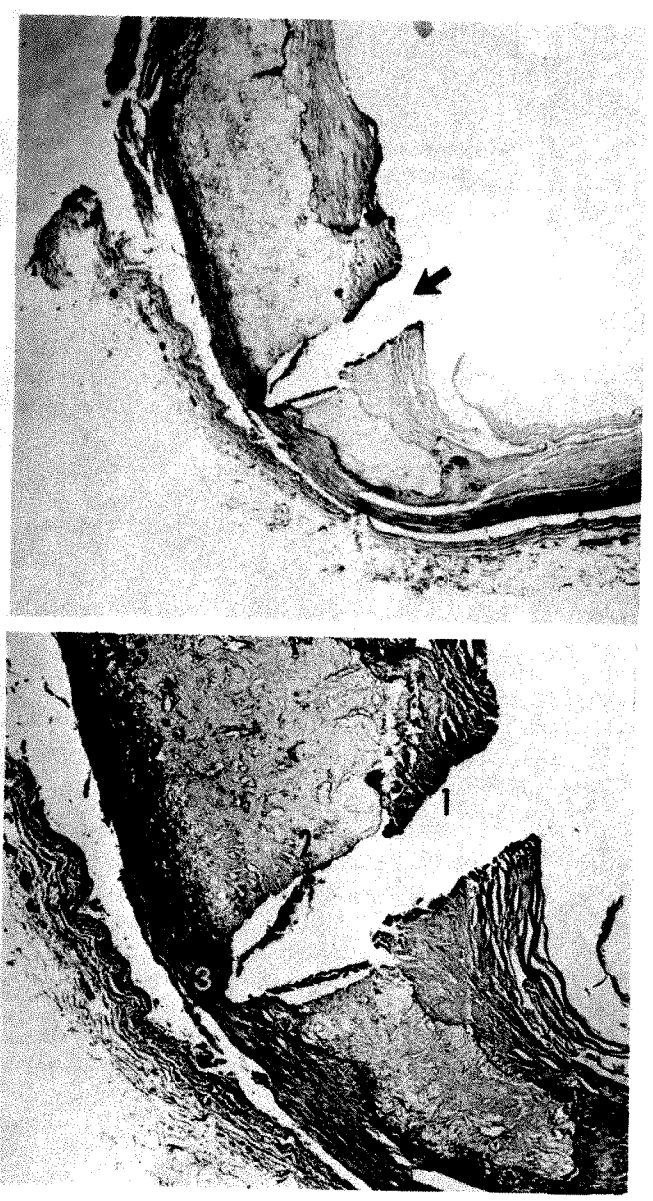

FIGURE 3. Histology of a laser injury to a fatty atherosclerotic plaque. The vessel was exposed to 5 J of total energy from a CO_2 laser under dry conditions. **Top,** low-power view (52×) of an atheroma showing a wedge-shaped incision (**arrow**). **Bottom,** higher magnification (119×) of the same artery showing the laser incision (1) and complete penetration of the fatty atheromatous core (2). The media has also been partly penetrated (3). Note the zone of complete vaporization of tissue and the zone of tissue burn along the laser path. (Hemotoxylin and eosin stain; reduced 30%.)

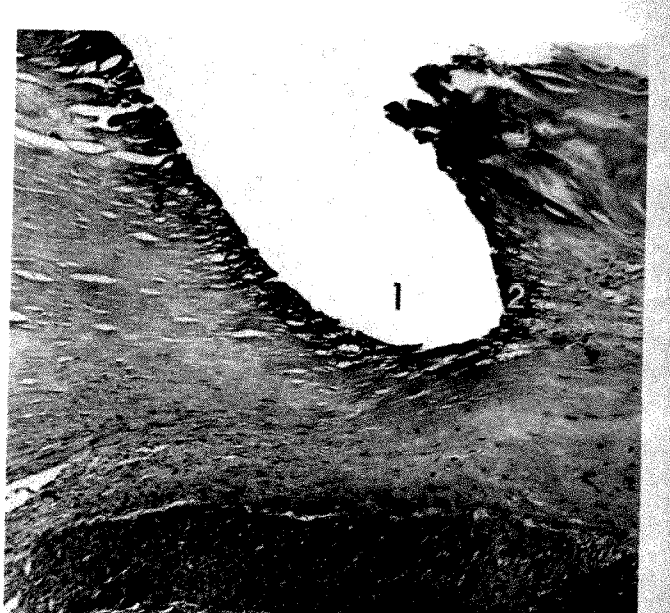

FIGURE 4. Histology of a laser injury to a fibrous atherosclerotic plaque. The vessel was exposed to 2 J of energy from a CO_2 laser under dry conditions. This section shows a zone of tissue vaporization in the path of the laser (1), a zone of adjacent tissue burn (2), and a zone of acoustic shock and injury that begins at the tissue burn edge and fades gradually into normal tissue structure (3). (Hematoxylin and eosin stain; magnified ×112, reduced 33%.)

FIGURE 5. Histology of a laser injury to a calcified fibrous atherosclerotic plaque. The vessel was exposed to 2 J of energy from a CO_2 laser under dry conditions. The calcified portion of the plaque is the area with more basophilic staining. The laser has penetrated the overlying fibrous tissue and has vaporized a portion of the calcified atheroma (**arrow**). (Hematoxylin and eosin stain; magnified ×67, reduced 33%.)

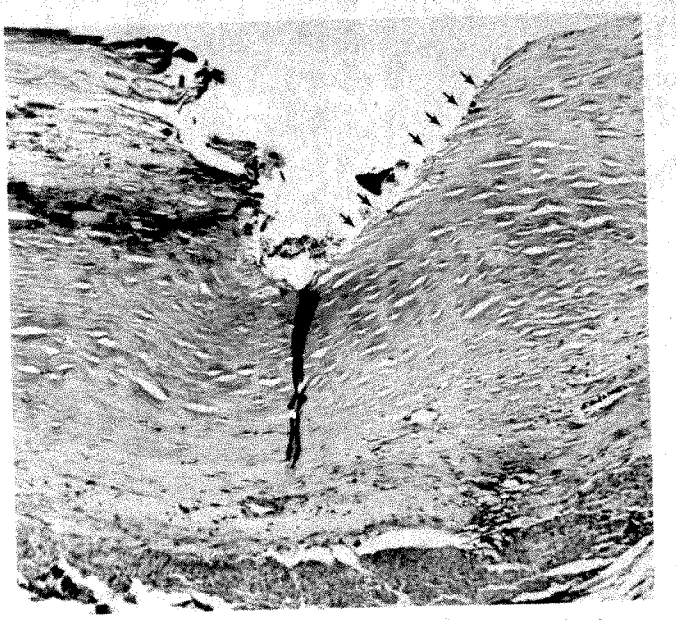

FIGURE 6. Histology of laser injury to a fibrous atherosclerotic plaque. The vessel was immersed in saline solution and exposed to 10 J of energy from a CO_2 laser. The incision penetrates the capsule and a portion of the fibromuscular atheroma. Note the absence of charring along the laser path (**arrows**). These effects differ from those when a plaque was lased under dry conditions (see Fig. 2 to 5). (Hematoxylin and eosin stain; magnified ×112, reduced 33%.)

undisturbed tissue and its precise outer border was difficult to define. Although the size of Zone 1 increased with applied energy, the surrounding zones of tissue injury appeared relatively constant in size. In addition, the histologic type of atherosclerotic plaque and the presence or absence of calcium did not appear to affect the magnitude of laser injury.

Effects of exposure to carbon dioxide laser radiation under saline solution: Twenty exposures were made and 30 tissue sections examined. Two important differences were noted between lasing under dry conditions and while immersed in saline solution. First, when immersed in saline solution more total energy was required to penetrate the plaque than was required under dry conditions. Arterial perforation could not be achieved even with the maximal power of 30 W and an exposure time of 0.5 second (15 J). With this amount of energy, only the plaque and underlying media were penetrated. This was approximately twice the energy required to perforate the artery under dry conditions. Second, microscopic examination of arterial segments

TABLE I Effect of Nd-YAG Laser Radiation Under Saline Solution on Human Atheromatous Plaques and Blood Vessels

Power (W)	Duration of Exposure (s)	Total Energy (J)	Plaque Penetration	Vessel Perforation
3.5	10	35	No	No
3.5	12	42	No	No
4.5	10	45	No	No
4.5	20	90	Yes	No
5.5	5	27.5	No	No
5.5	7	38.5	No	No
5.5	10	55	No	No
9	16	144	Yes	Yes
9	18	162	Yes	Yes
		Saline Solution + Cardiogreen		
3.5	3	10.5	No	No
3.5	5	17.5	No	No
3.5	28	98	No	No
		Saline Solution + Sudan Black		
2.5	2	5	Yes	No
2.5	10	25	Yes	No
4.5	10	45	Yes	No

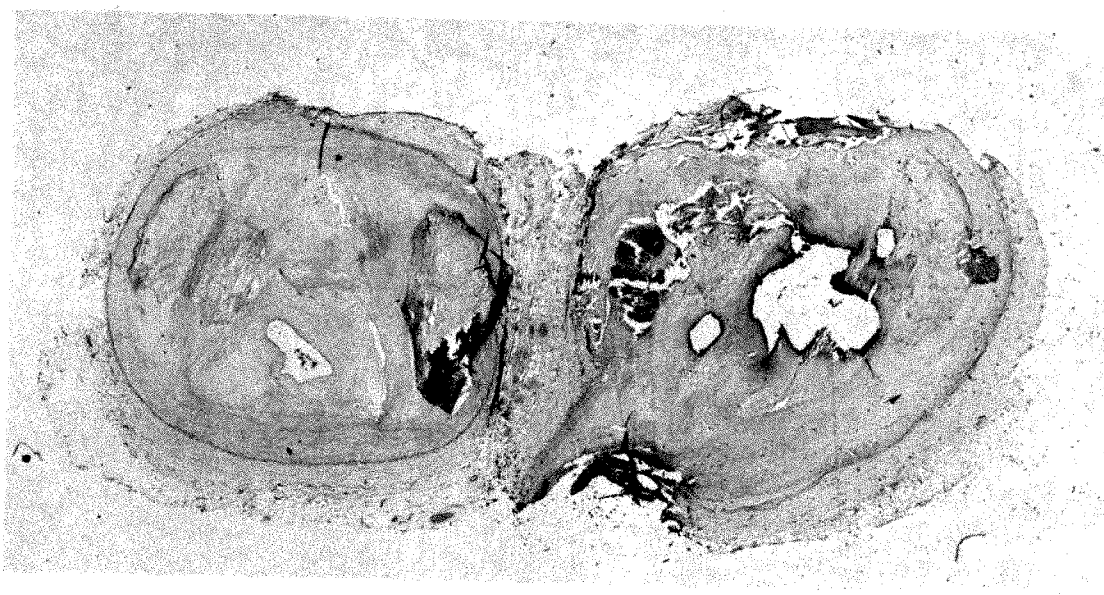

FIGURE 7. Establishment of a new lumen by exposure to Nd-YAG laser radiation in an occluded coronary artery immersed in saline solution. The artery was exposed to 71 J of energy. The artery was cut in half and the portion not exposed to laser radiation was used for comparison. A cross-section of the portion not exposed to laser radiation is shown on the **left** and of the portion exposed to laser radiation on the **right**. (Magnification ×25.)

exposed under saline solution revealed little to no charring along the incision edge of the laser (Fig. 6). When immersed in saline solution, small bubbles were produced during lasing.

Effects of exposure to Nd-YAG laser radiation under saline solution (Table I): Gross inspection of the occluded coronary artery segment exposed to Nd-YAG laser radiation demonstrated that the plaque was damaged but not penetrated when the total energy of exposure was less than 45 J. Between 55 and 90 J, successful plaque penetration occurred but without perforation (Fig. 7). Energy levels greater than 144 J consistently perforated. Because the energy required for plaque penetration was similar in plaques stained with cardiogreen, this dye did not enhance laser absorption. In contrast, staining with Sudan black did enhance laser absorption as the energy needed for successful plaque penetration decreased. Forty histologic sections were examined. Findings were similar to that described for the carbon dioxide laser when segments were immersed

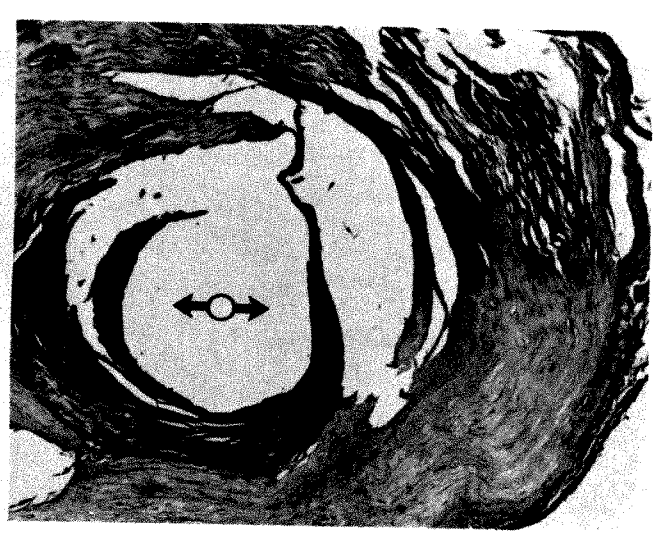

FIGURE 8. Establishment of a new lumen by exposure to Nd-YAG laser radiation in a totally occluded coronary artery immersed in saline solution. This artery was stained with Sudan black and then exposed to 25 J of energy. The **arrow** indicates the new lumen created by the laser. Note the incomplete vaporization of the plaque, with the injury in a concentric fashion sparing deep layers. (Magnification ×84, reduced 40%.)

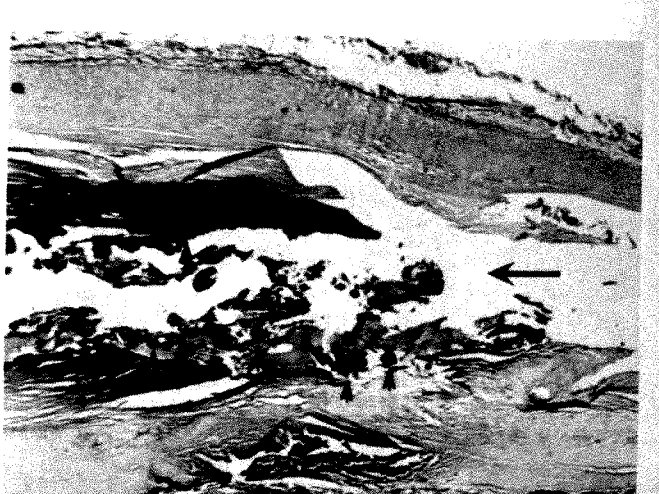

FIGURE 9. Longitudinal section of a human coronary artery showing recanalization of a previously occluded lumen (**arrow**). The plaque was exposed to Nd-YAG laser radiation with the artery immersed in blood. Recanalization required 56 J of energy. Impregnated hemoglobin pigment was seen along the lased lumen (**arrowheads**). (Magnification ×54, reduced 45%.)

TABLE II Effect of Nd-YAG Laser Under Whole Blood on Atheromatous Plaques and Blood Vessels

Power (W)	Duration of Exposure (s)	Total Energy (J)	Plaque Penetration	Vessel Perforation
1.2	160	192	No	No
1.9	140	266	No	No
2.4	5	12	Yes	No
2.4	11	26.4	Yes	No
3.5	7	24.5	Yes	No
3.5	9	31.5	Yes	No
5.0	4	20	Yes	No
5.0	5	25	Yes	No
5.0	13	65	Yes	No
5.0	16	80	Yes	No
5.0	19	95	Yes	No

TABLE III Effect of Argon Laser Radiation on Atheromatous Plaques and Blood Vessels Under Saline Solution and Whole Blood

Power (W)	Duration of Exposure (s)	Total Energy (J)	Plaque Penetration	Vessel Perforation
		Saline Solution		
1	60	60	No	No
2	15	30	Yes	No
3	5	20	Yes	No
4	5	20	Yes	No
		Whole Blood		
1	60	60	No	No
2	12	20	Yes	No
3	5	15	Yes	No
5	3	15	Yes	Yes

in saline solution. When Sudan black was used the amount of superficial tissue injury usually seemed greater (Fig. 8). Small bubbles were noted at the fiber tip during lasing.

Effect of exposure to Nd-YAG laser radiation under blood (Table II): In general, when immersed in blood, less total energy was required to successfully penetrate an atherosclerotic plaque as compared with immersion in saline solution. Two exposures were made at a much lower power (1.2 and 1.9 W), and despite prolonged exposure that delivered a total energy of 192 and 266 J, respectively, plaque injury occurred but successful penetration was not achieved. When the power was raised to more than 2 W, plaque penetration occurred with relatively short exposures (5 seconds or more) with a total energy of 12 to 95 J (Fig. 9). Fifteen histologic sections were examined. With one exception findings were similar to those described for the Nd-YAG or carbon dioxide lasers when segments were immersed in saline solution. The difference was that red blood cells and hemoglobin pigment were adherent to and impregnated within the zone of thermal-induced necrosis and coagulation. Small bubbles and vapor were again noted at the tip of the fiber during lasing.

Effects of exposure to Argon laser radiation under saline solution and blood (Table III): Under saline solution, 1 W could not penetrate the plaque after exposure for 60 seconds, but 2 or more W successfully penetrated the plaque with much shorter exposures (Table III). Under blood, 1 W could not penetrate the plaque after exposure for 60 seconds, whereas 2 or more W successfully penetrated with much shorter exposures. Fifteen tissue sections were examined, and findings were similar to these described for the other 2 laser sources. Small bubbles and vapor were noted when lasing under saline solution or blood.

Discussion

This study of the effect of laser radiation on atherosclerotic plaques was undertaken because certain properties of lasers suggested that they could be used to produce controlled tissue damage to blood vessels. These properties of lasers included (1) capacity to photocoagulate tissues, (2) preferential absorption by certain tissues, (3) control of energy output, (4) precise control of beam direction, (5) transmission by way of fiber optics through catheters designed for intravascular use, and (6) possible acceleration of tissue healing.[14–17]

These experiments showed that 3 different types of lasers were capable of damaging atherosclerotic plaques. Laser-radiation damaged plaques composed of either a central lipid core or fibrous proliferation. A moderate degree of calcification did not prevent laser-induced damage. These vessels were obtained at autopsy, and healing and inflammatory responses to laser radiation

were not evaluated. Additional studies will be needed to define chronic tissue responses occurring after laser radiation.

Power and duration of exposure to laser radiation emerged as important variables that could be regulated to produce predictable degrees of arterial injury. As a predictor of the degree of arterial injury, total energy delivered correlated better than either power or duration of exposure alone. Besides total energy, 2 other variables influenced magnitude of arterial injury: first, whether the arterial segment was exposed in air or immersed in saline solution or blood; and second, the type of laser source. Under dry conditions the carbon dioxide laser damaged atherosclerotic plaques with a minimum of 2.5 J of total energy. When the arterial segment was immersed in saline solution, similar damage to the plaque required a total energy >5 J. Compared with results using a saline medium, experiments conducted using the Nd-YAG laser and blood as the media demonstrated that blood-enhanced absorption as less energy was needed to produce plaque damage. Reasons for enhanced tissue absorption were not clear. However, one possibility was that hemoglobin pigments released from lased red blood cells adhered to and became impregnated in the vessel wall increasing laser absorption similar to that seen with Sudan Black. Experiments conducted under blood (Nd-YAG or Argon laser) or saline solution (Argon laser) suggested that a minimal power may exist below which successful plaque penetration did not occur even with prolonged lasing. A minimal amount of power may be necessary under other conditions with these lasers and also with the carbon dioxide laser, but was not apparent at the powers studied.

Several laser sources are available and differences between them may be important. The wavelength of the carbon dioxide is 10,600 nm whereas the wavelength of the Nd-YAG laser is 1,064 nm. The Argon laser has 2 principal wavelengths at 488 and 514 nm. Others have demonstrated that the wavelength of the laser beam is an important determinant of tissue absorption.[8] In these experiments, other than total energy required, no major differences among the 3 lasers were observed regarding plaque damage. Further studies are necessary to explore differences in energy requirements under various conditions among the 3 lasers. Also it seems clinically important that the fiberoptic material necessary to carry the high infrared frequency of the carbon dioxide laser is potentially water soluble and toxic.[18–20] This material is also expensive. Both the Nd-YAG and Argon lasers can be carried by optical fibers that are neither water-soluble nor toxic and they are relatively inexpensive. Both can be delivered through a catheter guided system to appropriate intravascular regions for application.[10,21] Some intermediary agents such as Sudan black but not cardiogreen may enhance surface absorption of the Nd-YAG laser. Enhanced surface absorption may be useful in localizing injury to the plaque and spare surrounding tissue. If this occurs the probability of perforation should decrease. Additional experiments will be needed using various dyes together with saline or blood media to define conditions that enhance superficial absorption and provide an adequate depth of penetration without perforation. Tissue damage produced with other lasers such as Argon and carbon dioxide may also be enhanced by intermediary agents.

In general, the histologic appearance of tissue damage created by the 3 lasers was similar. In each instance 3 zones of damage were noted consisting of an innermost zone of complete tissue vaporization, a second zone of thermal burning, and an outermost third zone of diffuse tissue disruption presumably caused by acoustic or shock injury. All these experiments were done with continuous wave lasers. A pulsed beam-type laser may produce different types of histologic injury.[15]

In conclusion, lasers can be used to damage atherosclerotic plaques. These techniques probably can be adapted to intravascular delivery of the laser beam through guidance systems similar to those used during percutaneous transluminal angioplasty. This experience encourages us to continue to explore further the potential uses of laser radiation to improve perfusion through obstructed arteries.

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Transluminal Laser Catheter Angioplasty

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The first transluminal laser angioplasty in animals is reported herein. An Argon laser and a specialized coronary arterial catheter with a fiberoptic wave guide were used. Immediate histologic changes consisted of a moderate degree of intimal necrosis and some loss of elastic tissue. At 5 days the intima was repaired, but focal elastic tissue loss persisted.

In 1978, one of us (DC) conceived of delivering laser energy from an external source through a fiberoptic wave guide to an intraluminal site to vaporize plaque and thrombus obstructions in vessels. Carbon dioxide laser energy was unsuitable because of the high heat generation and the lack of nontoxic wave guides. An Argon laser became the first choice because of its complementary absorption coefficient to hemoglobin and the availability of suitable wave guides. In vitro experiments and in vivo transluminal catheter angioplasty with use of Argon laser energy are described herein.

Methods

Energy source: A Coherent model 800 optical laser was utilized in preliminary in vitro experiments in the laboratories at Lenox Hill Hospital, New York City. This study confirmed the feasibility of vaporizing human thrombi, atherosclerotic plaques, and cartilage with Argon laser energy. Further experiments, using a Coherent model 1000 Argon laser and a delivery system consisting of an 85 μm core, 125 μm cladding silica fiber in a specialized intraarterial catheter, demonstrated that at 4.5 W output, a 1.0 cm tunnel could be bored in a fresh thrombus in 36 seconds. In an artificial vascular system filled with saline solution, an artificial clot subjected to laserization turned to vapor which appeared briefly as thousands of microscopic bubbles that rapidly disappeared in solution.

No analyses have as yet been performed, but because the constituents of a thrombus are mainly carbon and water, we speculate that the largest portion of this vapor is composed of steam and carbon dioxide. This finding is supported by the observation that the gas bubbles had a high degree of solubility in saline solution. We therefore do not anticipate gas embolization to be a problem in vivo. Spectroscopic analyses are underway to determine the exact composition of the vapor.

Another potential problem is heat generation. An exposure of 1.0 second at 3.5 W produces 3.5 J, or 0.84 Cal. With the exception of cartilage and the cores of neoplasms, the tissues of the body are richly invested with a capillary network which, like the cooling system of an internal combustion engine, contributes to thermal homeostasis. Prolonged exposure of tissues to ambient temperature above 44°C leads to irreversible precipitation of DNA and cytoplasmic proteins. The low levels of heat generation in laser angioplasty are unlikely to produce these conditions, especially with active capillary flow acting as a heat sink. We therefore do not believe that heat generation will present an insuperable problem in vivo.

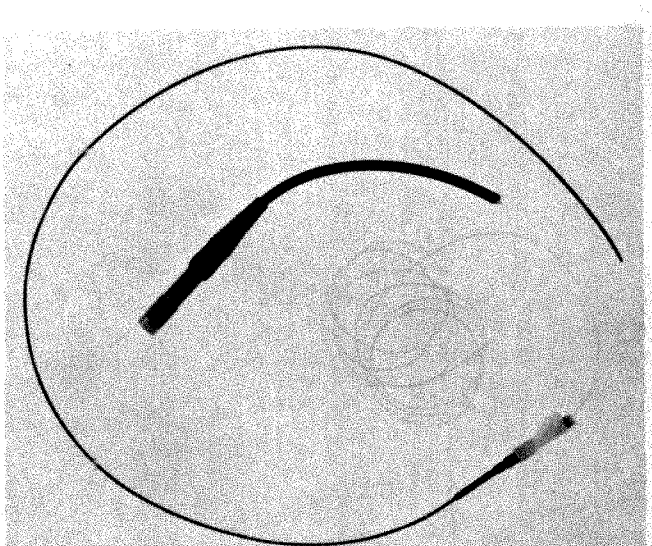

FIGURE 1. Model 4 French laser catheter with optical fiber in lumen. The thick end mates to coherent model 1000 Argon laser.

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The artificial thrombi produced here are histologically, but not biochemically, different from organized thrombi in vivo. The laser energy interacts with the physicochemical properties of the thrombi, and is independent of histologic differences. We are therefore cautiously optimistic about extrapolating in vitro results to an in vivo situation.

Delivery system: A laser catheter was invented by one of us (DC) and patented in June 1980 (U.S. Patent 4207874). This device may be briefly described as a fiberoptic wave guide incorporated into a catheter for conducting laser energy from an external source to an intraluminal site for the purpose of tunneling through obstructions of various types. An additional feature is a coherent fiberoptic bundle for endoscopic imaging. This catheter was previously described (by DC) at the International Laser Conference in Shanghai and Beijing in May 1980[1,2] (Fig. 1).

Animal experiments: Laser angioplasty was performed in acute experiments involving (1) the abdominal aorta of a rabbit, and (2) 2 femoral arteries of a dog. In these experiments the rabbit and dog were anesthetized with secobarbital and kept alive during the entire procedure. In the canine experiment, the right femoral artery was used on the first day and the left on the fifth day. An 8.0 cm length of artery was exposed, and a 1.0 cm segment was isolated between 2 ligatures. Human blood, 1.0 ml, and fresh thrombin, 0.2 ml, were injected into the lumen of this segment. After 5 minutes the ligatures were removed, the formation of a complete occlusive thrombus were verified by blanching, loss of distal pulsation, and by pressure tracings in the 4.0 cm of exposed distal artery (Fig. 2). The laser catheter, previously calibrated to deliver 3.0 W at the tip, was introduced proximally and advanced to abut the thrombus. The laser was then switched on.

In the case of the right femoral canine artery, the arteriotomy was repaired with 6-0 Tevdek® sutures and the wound closed. The rabbit was killed on the first day and the dog was killed on the fifth day.

Results

In all 3 instances, the 1.0 cm thrombi were vaporized in ±1.0 second. Patency of the arteries was demonstrated by (1) brilliant blue-green transillumination of the distal arteries which were previously dark; (2) resumption of blood flow and pulsation in the distal arteries; (3) pressure tracings (Fig. 2) in the right canine femoral artery; and (4) histologic sections (Fig. 3 to 5). Pressure tracings on electrocardiographic paper were obtained by inserting a needle transducer into the distal segment of the canine right femoral artery. Each 0.5 cm on the vertical axis represents 40 mm Hg. Baseline systolic pressure was 160 mm Hg. The pressure after angioplasty was 80 mm Hg. Because histologic sections 5 days later revealed complete absence of thrombus, we attribute the 80 mm decrease in pressure to narrowing of the proximal segment caused by repair of the arteriotomy and perhaps to immediate vascular wall edema from laser injury.

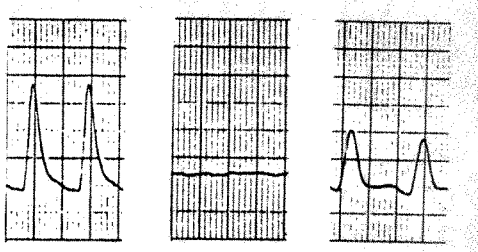

FIGURE 2. Pressure tracings of artery distal to thrombus.

By direct inspection, full flow was reestablished in the arteries distal to the thrombus after laser angioplasty. The blanched, collapsed arteries became full, red, and pulsatile.

In the canine experiment, the 5 postoperative days were uneventful. The animal was afebrile, had an enormous appetite, and was fully ambulatory with clinical evidence of excellent arterial perfusion of the operated leg.

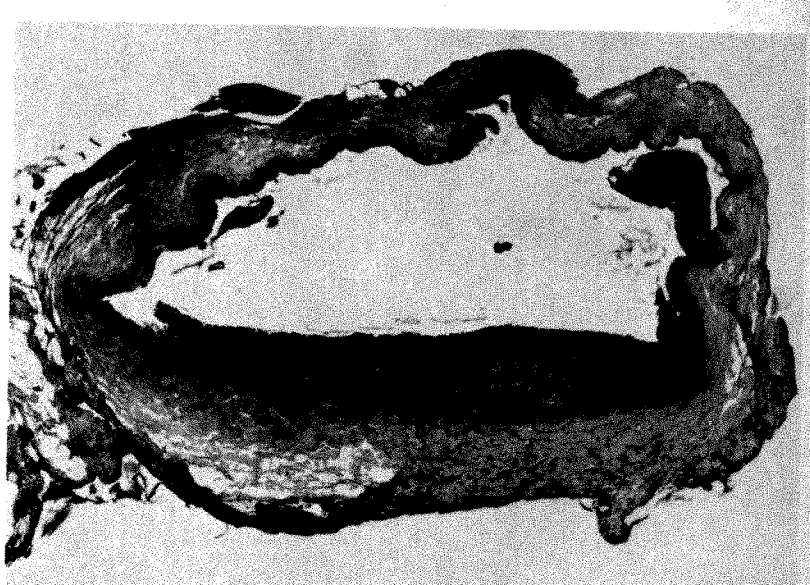

FIGURE 3. Segment of artery at thrombus site after laserization. Note complete absence of thrombus. (Hematoxylin-phloxine saffron stain; magnification X40, reduced 29%.)

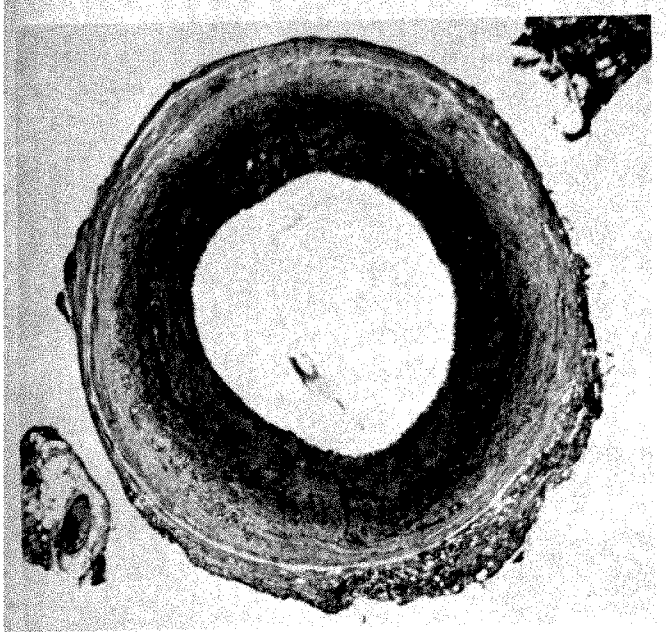

FIGURE 4. Canine femoral artery proximal to thrombus 5 days after laserization. (Hematoxylin-phyloxine saffron stain; magnification ×40, reduced 32%.)

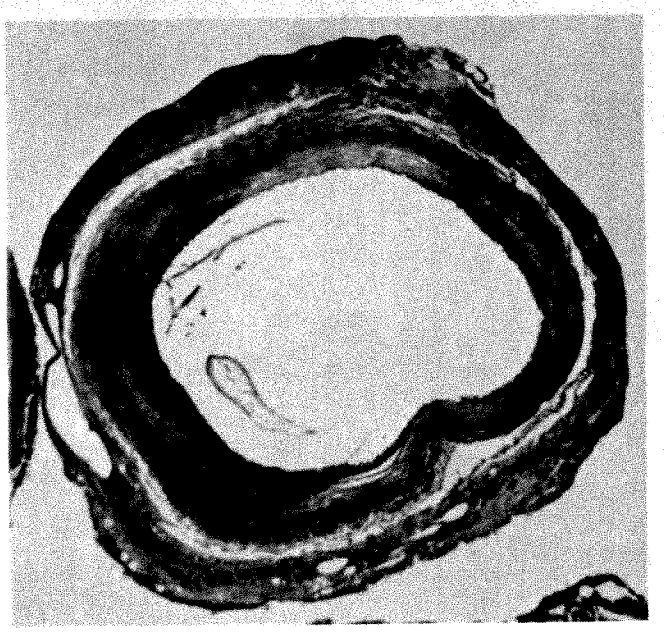

FIGURE 5. Canine femoral artery at the site of thrombus, 5 days after laserization. Note the focal loss of elastic tissue in the media, the absence of thrombus, and the intact endothelium. (Hematoxylin-phloxine saffron stain; magnification ×40, reduced 32%.)

Histology: In the acute experiments, sections of the arteries revealed a moderate degree of intimal necrosis and some loss of elastic tissue in the media in the region of the thrombus (Fig. 3). In the artery examined 5 days after laser angioplasty, the zone of focal medial damage measured 2.2 cm, extending 1.2 cm distal to the thrombus (Fig. 5). However, it is significant that (1) the thrombus was completely vaporized, (2) the intima was completely repaired in 5 days, although some focal elastic tissue loss persisted, and (3) no postlaserization thrombus had formed.

Discussion

Experience with vascular surgery since World War II has demonstrated that damage to the endothelial surface of arteries and veins is followed by deposition of fibrin and platelets, followed by complete endothelial repair in 2 days to 2 weeks, depending on the size of the denuded area.[3] Our finding of complete intimal repair in 5 days is consistent with this experience.

The question of distal embolization of debris arises. Previous in vitro experiments with an artificial vascular tree occluded by thrombus subjected to Argon laser angioplasty revealed total vaporization without debris formation; that is, the clot was turned directly into vapor appearing as thousands of microscopic bubbles that went into solution within 1 second. We believe it is reasonable to extrapolate these results to the in vivo situation. Moreover, there was no clinical evidence of distal embolization.

The discrepancy between the 36 seconds at 4.5 W exposure needed to bore a 1.0 cm tunnel in a free-standing clot and the 1.0 second at 3.0 W exposure needed to vaporize a 1.0 cm long intravascular clot may be explained by the fact that in the former instance the walls of the tunnel, being unsupported, kept collapsing and did not become rigid until carbonization occurred, whereas in the latter case, the vessel provided a supporting scaffold, and vaporization could proceed without continuing collapse of the tunnel walls.

From its inception 4 years ago, the concept of vaporizing intravascular plaques and thrombi by introducing laser energy through a wave guide in a flexible catheter has been shown feasible in in vitro and in vivo experiments.

Acknowledgment: We thank Percy Wendler, MD, for his invaluable assistance.

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Laser Coronary Angioplasty: Experience With 9 Cadaver Hearts

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Experience with laser angioplasty in 16 coronary arteries in 9 cadaver hearts is presented. Coronary obstructions were due to experimentally created thrombi as well as to naturally occurring calcified plaques. Successful laser angioplasty was achieved in 14 of 15 arteries. One artery was sacrificed to determine factors necessary for deliberate perforation of the arterial wall. This procedure required more than 30 seconds of laser energy at 3.0 W with the catheter tip almost perpendicular to the wall. Penetration of the arterial wall occurred only in the second left anterior descending artery which was plaque-occluded because of operator inexperience.

In a previous report,[1] we described the successful in vivo use of a laser catheter to recanalize arterial thrombotic obstructions in animals. We describe herein further experience using the same system in 16 coronary arteries in 9 cadaver hearts. The study was undertaken as a preliminary investigation leading to the eventual objective of performing percutaneous coronary angioplasty with the laser catheter in vivo, in acute and chronic, total and partial coronary artery occlusive disease.

Methods

Sixteen coronary arteries in 9 cadaver hearts were utilized. All arteries were dissected free from pericardial fat. There were 2 categories:

1. *Diseased arteries* (7): Three of the 7 were completely, and 4 were 70 to 80% (estimated cross-sectional area) obstructed by calcified plaque. This group required no further preparation.

2. *Nondiseased arteries* (9): Artificial thrombi were created in these as follows: A 1.0 cm segment of artery 1.5 to 2.0 cm distal to the ostium was isolated between 2 ligatures of 4-0 silk. A firm thrombus was created in this segment by injecting fresh blood into the lumen together with 0.05 ml of freshly prepared thrombin through a 26 gauge needle. Complete occlusion was then documented by inspection, palpation, and angiography (Fig. 2).

With use of the laser catheter[2,3] invented by one of us (DC) (U.S. patent 4207874) and a Coherent model 1000 Argon laser tuned to a tip output of 1.7 to 4.5 W, the thrombus or plaque was vaporized by introducing the catheter through the coronary artery ostium to the occlusion and switching on the laser in 0.5 to 1.0 second bursts. Between bursts of laser light, the catheter was manually advanced. Completion of tunneling was signalled by brilliant transillumination of the artery distal to the thrombus or plaque site (Fig. 1).

Patency of the artery was documented with repeat angiography (Fig. 2, right).

The arteries were then prepared for histologic examination.

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Results (Table I)

Diseased arteries (7): All 3 arteries totally occluded by calcified plaque were successfully canalized with exposures of 3.0 W at 46 seconds, 4.0 W at 42 seconds, and 4.0 W at 38 seconds (experiments 2 and 4).

Two of 2 arteries partially occluded by calcified plaque were canalized with exposures of 1.7 W at 12 seconds (experiment 1, left anterior descending artery [LAD]), and over a 5.0 cm length with 4.5 W at 48 seconds (experiment 8, LAD). In the latter instance, the artery that was previously impenetrable to a 3 French catheter easily admitted an 8 French catheter after laser tunneling.

One subepicardial dye extravasation occurred (experiment 2) when the catheter tip was inadvertently jammed into a shelf between plaque and wall.

In experiment 9, 2 ovoid calcified plaques were vaporized utilizing the following power variables: 8 by 3 by 2 mm plaque, 3.5 W at 3.0 seconds; and 7 by 3 by 2 mm plaque, 3.5 W at 2.5 seconds. Before vaporization, the plaques were seen as dark areas against a transilluminated (Fig. 1) background of normal vessel wall. After vaporization, the plaque areas transilluminated

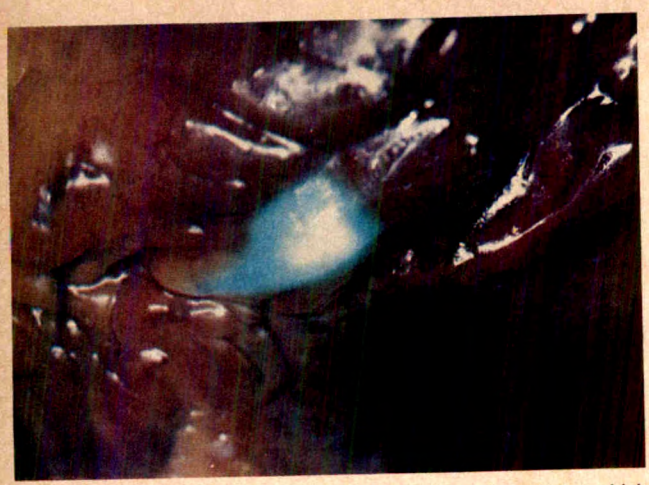

FIGURE 1. Coronary artery transilluminated by Argon laser beam which has vaporized the obstruction.

as well as normal vessel wall. This phenomenon will prove useful in the future use of the laser catheter to vaporize intraluminal plaques during open heart surgery.

Nondiseased arteries (9): The artificially created thrombi were vaporized with no difficulty at exposures ranging from 1.7 W at 4.0 seconds to 4.5 W at 1.0 second. This was accomplished in 8 of 8 arteries.

One artery (experiment 5, right coronary) was used to ascertain exposure time needed to deliberately perforate the wall. With the catheter tip positioned at 80° to the wall, perforation occurred with an exposure of 3.0 W at 30.8 seconds (92.5 J).

Discussion

Successful laser angioplasty was achieved in 8 of 8 coronary arteries that were artificially occluded with fresh thrombi, and in 6 of 7 coronary arteries that were

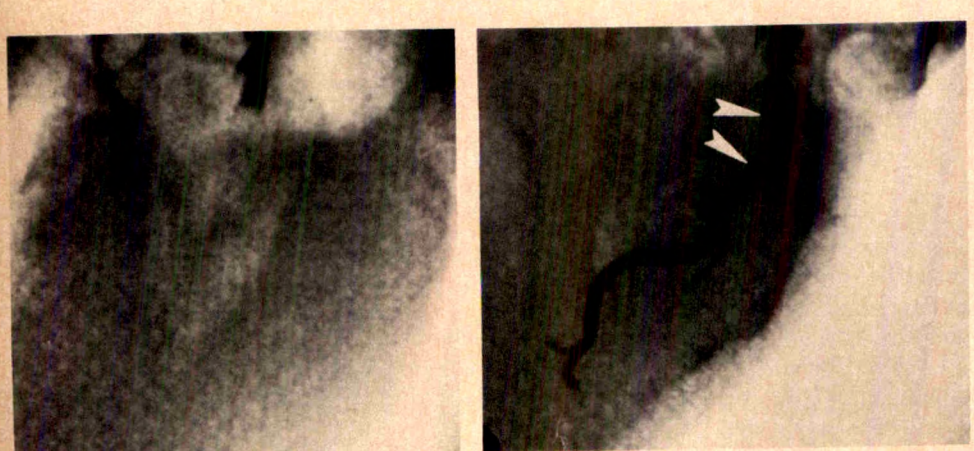

FIGURE 2. Left, angiogram of an obstructed LAD. **Right,** angiogram of the same LAD after laser vaporization of thrombus (**between the 2 arrows**). Note the excellent flow distal to the site of obstruction. The diagonal filling defect may represent incomplete vaporization.

TABLE 1 Results in Coronary Arteries Treated With Laser Angioplasty

Exp		Thrombus	Plaque	Watts	Seconds	Remarks
1	LAD		+	1.7	12	70% estimated cross-sectional area obstruction over 2 cm length. Artery was curved. No perforation
	RC	+		1.7	4	Tunneling complete
2	LAD		+	3.0	10	Subepicardial dye extravasation. Catheter tip caught on shelf
	RC		+	3.0	46	100% occlusion. Angiogram confirmed patency
3	LAD	+		4.0	2	Tunneling complete
	RC	+		4.0	2	Tunneling complete
4	LAD		+	4.0	42	100% occlusion. Tunneling complete
	RC		+	4.0	38	100% occlusion. Tunneling complete
5	LAD	+		3.0	3	Tunneling complete
	RC			3.0	30.8	Deliberate perforation of wall by placing catheter 80° to wall
6	LAD	+		3.5	1	Tunneling complete
	RC	+		3.5	1.5	Tunneling complete
7	LAD	+		4.0	1	Tunneling complete
	RC	+		4.0	1	Tunneling complete
8	LAD		+	4.5	48	Artery 80% estimated cross-sectional area obstruction along entire length. 3F catheter would not pass. 5 cm tunnel achieved in 48 seconds. 8F catheter would pass
9	RC		+	3.5	3.0	8 × 3 × 2 mm ovoid plaque vaporized
				3.5	2.5	7 × 3 × 2 mm ovoid plaque vaporized. Area then transilluminated normally

Exp = experiment; RC = right coronary artery.

FIGURE 3. Coronary artery at thrombus site. Note that the thrombus has been completely vaporized with minimal damage to the intima. (Hematoxylin-phloxine-saffron stain. Magnification ×40, reduced 30%.)

naturally occluded, totally and subtotally, with calcified plaque.

The 1 failure in the diseased arteries was due to unfamiliarity with catheter control, causing the catheter tip to be inadvertently insinuated between a shelf plaque and the wall (experiment 2).

In the same experiment, the right coronary artery, completely occluded by calcified plaque, was approached with more careful laser catheter control; that is, the catheter was so manipulated that it was coaxial with the artery during delivery of the laser energy. The plaque was tunneled through by an exposure of 3 W at 46 seconds. Excellent distal runoff was demonstrated with angiography. There was no penetration of the arterial wall.

Why did deliberate perforation of the arterial wall require 30.8 seconds at 3.0 W and inadvertent perforation occur at 3.0 W and 10 seconds? In our opinion, the 20-second differential is due to the fact that in the latter instance the catheter tip was being forcibly pushed against the wall.

Because many thrombotic total and subtotal coronary artery occlusions average 1.0 cm in length, and can be vaporized in 1 second at 4.5 W, it is doubtful that perforation of the arterial wall will be a significant problem in later attempts at in vivo laser coronary artery angioplasty.

This is particularly true because the design of the laser catheter will permit its use only when coaxial with the lumen of the vessel.

In this regard, even total obstructions of calcified plaque (experiment 4) can be vaporized with no danger of perforation through careful manipulation of the catheter.

The histologic section (Fig. 3) demonstrated complete vaporization of thrombus and minimal damage to intima. In previous animal experiments,[1] intimal damage was completely repaired in 5 days, and no postlaserization thrombosis occurred. On that basis, one might expect that with use of antiplatelet and anticoagulant drugs, complete reendothelization would occur within 1 week without postangioplasty thrombosis.

Conclusions: The foregoing data in the pilot animal experiments and in 16 coronary arteries lead us to conclude that (1) damage to intima and accidental perforation of arterial wall by the laser catheter are controllably low incidence risks, and (2) percutaneous laser coronary artery angioplasty under fluoroscopic image intensifier guidance may be a clinical reality in the near future.

Acknowledgment: We are indebted to Milda Brodi Goldstein and James McCrossan for invaluable technical assistance. The Coherent model 1000 Argon laser was supplied through the courtesy of Woody Woodward, Coherent Radiation, Palo Alto, California.

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Prospective Evaluation of Radionuclide Angiocardiography For the Diagnosis of Coronary Artery Disease

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This investigation assesses prospectively the accuracy of rest and exercise radionuclide angiocardiography (RNA) in detecting coronary artery disease (CAD). By retrospective analysis of 496 patients, optimal RNA criteria were determined for the presence or absence of CAD. Multivariate analysis of patients with normal coronary arteries on catheterization provided a formula to predict normal exercise ejection fraction (EF) in a given patient. The presence of CAD was indicated by 1 or more of the following RNA measurements: (1) rest EF <0.50, (2) exercise EF at least 0.06 less than the predicted value, (3) exercise increase in end-systolic volume >20 ml, (4) exercise-induced wall motion abnormality. The absence of CAD was indicated by the absence of all 4 criteria. After applying these criteria to 221 consecutive patients, the RNA determinations were compared with the catheterization determinations. Significant CAD was present in 71% of the patients studied. The sensitivity of the test was 0.87 and the specificity 0.54. Thus, because of its high sensitivity, RNA is of value in screening patients under consideration for cardiac catheterization. No patient with significant left main coronary narrowing and only 4 of 65 patients with 3-vessel disease were misdiagnosed. The poor specificity of the test, however, limits its overall accuracy.

Noninvasive radionuclide techniques for measuring left ventricular function at rest and on exercise have been advocated for diagnosis of CAD.[1–4] These early studies used arbitrary criteria for differentiating an abnormal from a normal study. More recently, the optimal criteria for the detection of CAD by rest and exercise radionuclide angiocardiography in patients being evaluated for chest pain were retrospectively determined and applied to a large patient population.[5] The rest and exercise radionuclide study had a sensitivity of 0.90 and a specificity of 0.58 in 496 retrospectively studied patients. However, it is important to apply criteria optimal for defining a normal and abnormal test in a population other than that used to derive the criteria. Therefore, the purpose of this study was to apply these diagnostic criteria prospectively to a large group of consecutive patients undergoing both rest and exercise radionuclide angiocardiography and coronary angiography.

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Methods

Study population: From January 1, 1980 through December 31, 1980, 693 patients underwent initial cardiac catheterization at Duke University Medical Center for the evaluation of CAD. Of this group, 72 patients had a history of valvular or congenital heart disease or previous cardiac surgery. Of the remaining 621 patients, 233 underwent rest and exercise RNA. Twelve patients were excluded because of inability to exercise for at least 5 minutes or achieve an exercise end point of chest pain, electrocardiographic change, or 85% of the maximal predicted heart rate for age. Therefore, the population studied included 221 patients.

Radionuclide angiocardiographic technique: RNA was performed at rest and on exercise exactly as in our earlier retrospective study.[5] A first transit technique was employed using a multicrystal gamma camera (System 77, Baird Corporation) and an intravenous bolus of 15 mCi of technetium-99m pertechnetate. A resting study was performed with the patient sitting erect on a bicycle ergometer (Fitron-Lumex). Exercise was begun at a work load of 200 kpm/min and was increased by 100 kpm/min each minute. End points used to time the exercise study included angina, electrocardiographic evidence of ischemia, 85% of the maximal predicted heart rate, or severe fatigue or dyspnea.

Measurements determined included left ventricular ejection fraction, end-diastolic volume, and end-systolic volume.

The validity and reproducibility of these measurements has been previously established.[6–8] Static and cineangiographic images of left ventricular wall motion allowed qualitative analysis of the anterior, apical, and inferior walls of the left ventricle. Wall motion assessment was derived from the consensus of at least 4 experienced observers without knowledge of the patient's clinical history or coronary angiographic results.

Optimal diagnostic criteria: From a retrospective analysis of 496 patients, optimal criteria for diagnosing the presence of CAD had been derived from measurements of left ventricular function at rest and during exercise.[5] The abnormality of resting ventricular function providing the greatest diagnostic information was an ejection fraction <0.50. Multivariable analysis in 60 patients with chest pain and normal coronary arteries demonstrated that sex, resting ejection fraction, and rest-exercise change in end-diastolic volume were major predictors of the magnitude of normal increase in left ventricular ejection fraction during exercise.[9] The equations used to predict change in ejection fraction with exercise (ΔEF) were as follows: For men, $\Delta EF = 0.45 - 0.5$ (EF at rest) $- 0.002$ (ΔEDVI), and for women, $\Delta EF = 0.385 - 0.5 \times$ (EF at rest) $- 0.002$ (ΔEDVI). An exercise ejection fraction at least 0.06 less than predicted was then determined as 1 of the optimal criteria for the detection of coronary disease. An increase in end-systolic volume >20 ml with exercise and the appearance of an exercise-induced wall motion abnormality were also included as optimal criteria. The relative sensitivity and specificity of each of these criteria were analyzed separately and together in this prospective study.

Statistical analysis: Chi-square analysis was employed to compare the clinical characteristics of the 221 patients in this prospective study with the 621 patients who underwent cardiac catheterization in 1980. A similar comparison was made with the 496 patients from whom the optimal diagnostic criteria were derived.[5]

Results

Clinical characteristics: The clinical characteristics of the prospective group (Table I) were similar to those of all patients with chest pain who underwent initial cardiac catheterization at Duke University Medical Center during 1980. The prospective group was also similar to the 496 patients described in our retrospective study.[5] The incidence of systemic hypertension was significantly higher in patients studied in 1980, but no differences existed in sex or age distribution or frequency of smoking or diabetes. The types and severity of chest pain and extent of CAD also were similar.

TABLE I Comparison of Clinical Characteristics and Disease Severity in Patients Evaluated for Chest Pain Before and After January 1, 1980

	221 Patients With Cath & RNA, 1980 (%)	621 Patients With Cath, 1980 (%)	496 Patients With Cath & RNA, 1977–1979 (%)
Clinical characteristics			
Males	75	73	75
Age (yr)			
<40	8	8	12
>70	0	0.5	1
Hypertension	48	47	35*
Diabetes	12	11	9
Smoking	65	69	70
Chest pain			
Typical	62	66	60
Atypical	34	32	34
Nonanginal	4	2	6
NYHA class IV	54	56	51
Progressive	36	44	33
Coronary anatomy			
Normal	21	21	15
Insignificant	7	8	10
1-vessel	18	16	19
2-vessel	21	21	24
3-vessel	29	32	26
Left main	3	5	6

* $p < 0.0002$. Cath = cardiac catheterization; NYHA = New York Heart Association; RNA = rest and exercise radionuclide angiocardiogram.

Correlation of RNA results with presence of CAD (Table II): The resting RNA ejection fractions of patients with and without significant CAD are depicted in Figure 1. Only 1 patient without CAD had a resting ejection fraction <0.50 (specificity 0.98). The sensitivity for this criterion alone, however, was only 0.23 (Table II).

TABLE II Prevalence of Positive Tests in Patients With and Without CAD

	CAD Absent			CAD Present				
	Prevalence			Prevalence				
	Normal (n = 47)	Insignificant (n = 16)	Specificity	1V (n = 40)	2V (n = 46)	3V (n = 65)	LM (n = 7)	Sensitivity
Rest EF <0.50	0.02	0	0.98	0.18	0.22	0.31	0	0.23
Rest EF ≥0.50	n = 46	n = 16		n = 33	n = 36	n = 45	n = 7	
and								
A. Ex EF at least 0.06 <predicted	0.39	0.31	0.63	0.70	0.69	0.76	0.86	0.73
B. Ex-induced wall motion abnormality	0.22	0.19	0.79	0.52	0.50	0.71	1.0	0.61
C. Increase in ESV >20	0.11	0.06	0.90	0.27	0.39	0.67	1.0	0.50
A and B and C	0.04	0.06	0.94	0.21	0.31	0.47	0.86	0.37
A or B or C	0.48	0.38	0.55	0.76	0.75	0.91	1.0	0.83
Rest EF <0.50	n = 47	n = 16		n = 40	n = 46	n = 65	n = 7	
or								
A or B or C	0.49	0.38	0.54	0.80	0.80	0.94	1.0	0.87

EF = left ventricular ejection fraction; ESV = left ventricular end-systolic volume; Ex = exercise; LM = left main coronary artery disease; V = vessel.

The differences from predicted exercise ejection fraction for patients with resting ejection fractions >0.50 are illustrated in Figure 2. Differences in patients with CAD tended to fall further from predictions, but significant overlap existed between the 2 groups. Using the criterion of 0.06 or more below predictions to indicate disease, the specificity of exercise ejection fraction alone was 0.63 and the sensitivity was 0.73 (Table II).

The changes in end-systolic volume with exercise in the patients with resting ejection fraction >0.50 are depicted in Figure 3. Again, much overlap was observed between patients with and without disease. A cutoff of a 20 ml increase provided a specificity of 0.90 and a sensitivity of 0.50 for this criterion alone (Table II).

Of the 183 patients with a resting ejection fraction >0.50, an exercise-induced wall motion abnormality was present in 61% of patients with disease (sensitivity) and absent in 79% of patients without disease (specificity). If all 3 exercise criteria were required to define CAD presence, the specificity increased to 0.94 and the sensitivity decreased to 0.37. Requiring any 1 of the 3 exercise criteria decreased the specificity to 0.55 and increased the sensitivity to 0.83 (Table II).

The greatest sensitivity was observed for the entire group when any 1 of the 4 criteria (resting EF <0.50, difference in exercise EF of at least 0.06 less than predicted, increase in end-diastolic volume >20 ml, or exercise-induced wall motion abnormality) was present. Of the patients with CAD, 87% were identified correctly using these criteria. Moreover, no patient with significant left main coronary narrowing and only 4 of 65 patients with 3-vessel disease were incorrectly diagnosed. The specificity of the test using all 4 criteria, however, was 0.54 as only 34 of the 63 patients without significant disease had a negative result.

False-positive findings: By requiring only 1 of 4 criteria to determine the presence of CAD, 29 (46%) of the 63 patients without CAD were misdiagnosed. Seventeen (55%) of 31 women and 12 (38%) of 32 men without CAD were designated as having CAD by 1 or more of the 4 criteria. Twelve of the 29 false-positive findings were positive only by an exercise ejection fraction of 0.06 or more below predicted. Two false-positive results occurred solely because of an exercise increase in end-systolic volume >20 ml. Three other false positives resulted from isolated exercise-induced wall motion abnormalities. One false positive occurred from a low resting EF. One patient with a false-positive finding had a positive exercise ejection fraction and exercise end-systolic volume. Seven false-positive findings were associated with both exercise-induced wall motion abnormalities and exercise ejection fractions 0.06 or less than predicted. Three false-positive results were positive for all 3 exercise criteria. The age distribution of the patients with false-positive findings (range 27 to 62 years, mean 49.8) was representative of the entire group studied (range 27 to 70 years, mean 51.6). The frequency of systemic hypertension, diabetes mellitus, and smoking in the patients with false-positive results was similar to that in all 221 patients. Typical chest pain was less common (5 of 29) and nonanginal (5 of 29) and atypical (19 of 29) chest pain were more common among the patients with false-positive findings

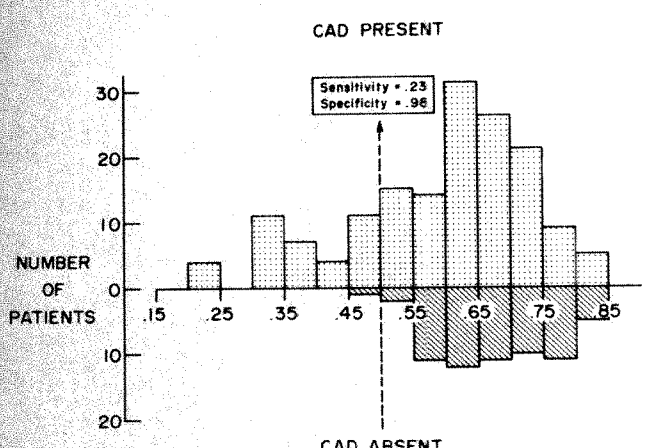

FIGURE 1. Distribution of rest ejection fractions in 221 patients with and without coronary artery disease.

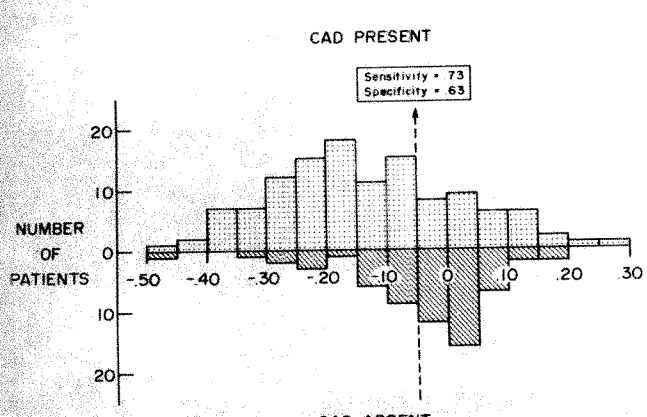

FIGURE 2. Distribution of differences from predicted exercise ejection fraction in 183 patients with resting ejection fractions >0.50.

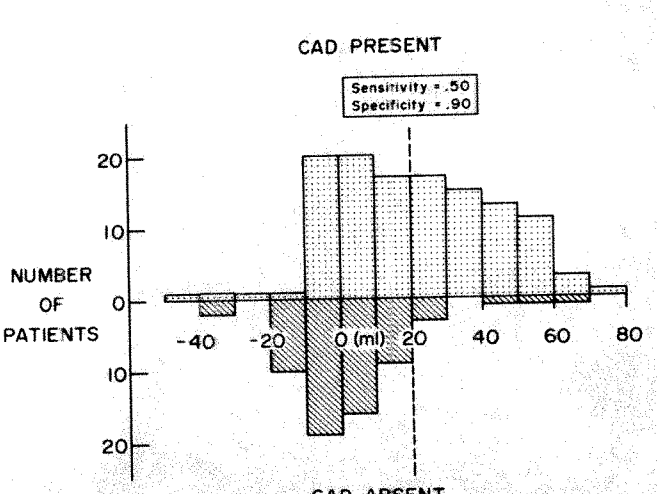

FIGURE 3. Distribution of changes in left ventricular end-systolic volume on exercise in 183 patients with resting ejection fractions >0.50.

TABLE III Overall Accuracy of Rest and Exercise Radionuclide Angiocardiography in the Diagnosis of Coronary Artery Disease: A Prospective Study

	165 Men	56 Women	221 Patients
Disease prevalence	0.82	0.45	0.71
Sensitivity	0.87	0.84	0.87
Specificity	0.63	0.45	0.54
Predictive value			
Positive test	0.91	0.55	0.83
Negative test	0.51	0.78	0.60
Efficiency	0.82	0.63	0.77

than in the entire group. Of the 29 patients with false-positive findings, 22 achieved 85% of the maximal predicted heart rate for the exercise study (compared with 105 of 221). The mean heart rate and systolic blood pressure achieved during exercise in the patients with false-positive findings were 153 beats/min and 164 mm Hg, compared with 144 beats/min and 156 mm Hg for the whole group. Six of 29 had chest pain (63 of 221), and 3 of 29 (69 of 221) exhibited electrocardiographic changes during exercise. The mean exercise work load was 690 kpm/min for the patients with false-positive findings and 710 kpm/min for the entire group.

Differences between men and women: RNA diagnosis of CAD was more accurate in men than in women (Table III). The sensitivity of the test using the 4 criteria was similar in both men and women (0.87 and 0.84, respectively), but the specificity in women was 0.45 compared with 0.63 in the men. The disease prevalence was lower in the women (0.45 for women versus 0.82 for men). A positive test was highly predictive of the presence of disease in men (0.91) but less predictive in women (0.55). A negative test had a higher predictive value in women (0.78) than in men (0.54). Of the men, 82% were correctly classified by the test, whereas only 63% of the women were correctly identified.

Influence of other factors on diagnostic accuracy: Twenty-one patients (9.5%) were taking propranolol at the time of study. Only 2 patients receiving this medication were misdiagnosed (2 false-positive results). Four patients were found to have a prolapsing mitral valve; none of these 4 had significant CAD. Two of these patients were correctly diagnosed as having no CAD and the other 2 had false-positive exercise ejection fractions.

Discussion

Early studies using RNA at rest and on exercise demonstrated that in normal subjects ejection fraction increased with exercise, whereas in patients with ischemia from CAD, ejection fraction decreased with exercise.[1,10] Further studies have shown that increases in left ventricular end-systolic volume[11,12] and the development of wall motion abnormalities[2–4] with exercise can also be sensitive and specific indicators of significant CAD. These studies, however, involved small groups of patients, often including asymptomatic volunteers. From our earlier experience with 496 patients undergoing cardiac catheterization for chest pain, we combined resting ejection fraction and exercise-induced changes in ejection fraction, end-systolic volume, and wall motion to determine optimal RNA criteria for diagnosis of CAD.[5] The sensitivity and specificity determined in this prospective study were similar to those derived in that retrospective analysis.

An overall test sensitivity of 0.87 compares favorably with other noninvasive techniques for detecting CAD. Electrocardiographic treadmill testing in large groups of patients presenting with chest pain has been shown to have a sensitivity of 0.70 to 0.80.[13–15] In 187 patients at our institution undergoing both treadmill testing and rest and exercise RNA, the sensitivity of RNA was 0.86 compared with 0.73 for treadmill testing.[5] Thallium myocardial perfusion imaging has been shown to have a sensitivity of 0.56 to 0.93.[14–19] Thallium imaging was not employed in the present study, and a direct comparison cannot be made. Nevertheless, rest and exercise RNA appears to offer a sensitivity for the detection of CAD that surpasses that of treadmill testing and at least equals that of thallium imaging.

The major limitation of rest and exercise RNA is the low specificity of 0.54. Early reports of specificity for RNA[2–4] were much higher than our present findings but were not determined from a large group of consecutively studied patients. Caldwell et al,[18] in an analysis of 52 patients, described a similar level of specificity (0.54) for RNA. The specificity for thallium imaging in the same patients with 1.0. Although few other reports of thallium imaging attest to perfect specificity, specificity of thallium imaging commonly exceeds 0.85.[14–19] The specificity of electrocardiographic treadmill testing ranges between 0.64 and 1.0.[13–17] In our own analysis of 187 patients with both electrocardiographic treadmill testing and radionuclide angiocardiography, the specificity of treadmill testing was 0.80 compared with 0.61 for RNA.[5] Thus, the specificity of rest and exercise RNA is less than attainable by treadmill testing or thallium imaging.

The poor specificity of the test may be due in part to the reliance upon measurements of global function. Conditions other than CAD may display global abnormalities, whereas CAD has been expected to exhibit more regional dysfunction.[20] The use of wall motion analysis alone, however, in this study failed to identify 40% of patients with significant CAD. Thus, until newer techniques for objectively measuring segmental wall motion are shown to be sensitive as well as specific, measurements of global function will be necessary. The specificity of the test may improve with better understanding of the normal ventricular response to exercise. In 229 patients chosen for defining RNA exercise criteria, inclusion of sex, resting ejection fraction, and change in end-diastolic volume with exercise to predict exercise ejection fraction improved the test specificity from 0.60 to 0.76 without altering the sensitivity.[5] A diminishing ejection fraction response to exercise with increasing age also was recently described.[21] Age, however, was not a major factor affecting specificity in the present study.

RNA test specificity was especially poor in women, as more than half of the women without CAD had positive test results. The incidence of positive tests in patients without CAD was higher for women in both the prospective and retrospective studies. In neither study was the incidence of false-positive tests in women significantly higher than that in men. If both studies are combined, the 56% (44 of 79) incidence of positive tests in women without CAD was significantly higher ($p = 0.044$ by chi-square analysis) than the 40% (35 of 87) incidence in men without CAD. The strength of this observation will depend on the results in a larger number of patients, but a fundamental difference in left ventricular response to exercise may exist between men and women. Similar problems with test specificity in women have been observed with electrocardiographic treadmill testing.[22] Why women should respond differently to exercise than men is not known, but the high incidence of "abnormal" studies in women without CAD may reflect the presence of a cardiac abnormality not detected by coronary angiography, such as exercise-induced coronary spasm. Whatever unknown factors may be involved, rest and exercise RNA is of limited value as a diagnostic test in women.

Thus, because of its low specificity, rest and exercise RNA is not recommended as a screening test for an asymptomatic population or as a diagnostic test for women with chest pain. However, because of its high sensitivity, especially for severe CAD, it is recommended for men with chest pain who are being considered for cardiac catheterization. If a positive RNA had been a requirement for catheterization in the 165 men in the present study, 37 patients (22%) would not have undergone catheterization. Seventeen patients with significant CAD would not have been detected, but 13 of them had only 1- or 2-vessel disease. No patient with significant left main narrowing and only 4 of the 57 patients with 3-vessel disease would have been missed. Because an occasional patient with 3-vessel disease will have a normal rest and exercise RNA, we do not at this time advocate requiring a positive RNA before proceeding to angiography. Nevertheless, in our experience no patient with any extent of CAD who has had normal rest and exercise findings on RNA has died during follow-up from 6 to 60 months. Preliminary information suggests that patients with left ventricular dysfunction during exercise may be more at risk for myocardial infarction or death than are patients with a normal response, irrespective of the number of vessels diseased. Therefore, the more important clinical use of measurements of ventricular function during rest and exercise may be the selection of patients who would benefit most from myocardial revascularization.

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Serial Right Ventricular Thallium-201 Imaging After Exercise: Relation to Anatomy of the Right Coronary Artery

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The relation of the appearance of the right ventricle on serium thallium-201 myocardial imaging to coronary artery anatomy was examined in 88 consecutive patients undergoing exercise thallium-201 testing and coronary angiography for the evaluation of chest pain. Transient defects in the right ventricle were found in 8 patients. All had high grade (≥90%) stenosis of the proximal right coronary artery. Nonvisualization of right ventricular (RV) activity occurred in 10 patients. Nine of the 10 (90%) had significant (≥50% stenosis) disease of the proximal right coronary artery and 7 (70%) had high grade stenosis. The right ventricle appeared normal in 70 patients. Twenty-nine (41%) of these patients had significant proximal right coronary artery disease. Right ventricular appearance was not affected by the presence or absence of disease of the left anterior descending or left circumflex artery or by the appearance of the left ventricle.

Thus, with serial RV thallium-201 myocardial imaging after exercise, we found that (1) RV transient defects suggest the presence of high grade proximal right coronary artery stenosis, (2) nonvisualization of RV activity also predicts significant proximal right coronary disease, and (3) the right ventricle frequently appears normal despite proximal right coronary artery disease and therefore this finding does not exclude such disease.

Several recent reports[1–3] have described an abnormal RV ejection fraction response to exercise in the presence of proximal right coronary artery disease. This response may result from inadequate RV perfusion during exercise with resulting RV ischemia. Serial thallium-201 imaging is useful in the evaluation and perfusion and detection of ischemia. However, the relation between RV perfusion, as assessed by thallium-201 imaging, and right coronary artery anatomy has not been analyzed in detail. Although isolated cases of abnormal RV thallium-201 activity associated with proximal right coronary artery disease have been reported,[4] previous studies of myocardial perfusion using thallium-201 have concentrated on left ventricular activity.

In the present study we assessed the relation of serial RV thallium-201 distribution and redistribution to right coronary artery anatomy in 88 consecutive patients after upright exercise. In addition, because the left ventricular wall is generally supplied by the right coronary artery, thallium-201 distribution in the left ventricular inferior wall was also examined.

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Methods

Patient population: Serial thallium-201 imaging was performed in 88 consecutive patients admitted for coronary and left ventricular cineangiography for the evaluation of chest pain. Radionuclide imaging and catheterization procedures were performed within 2 weeks of each other. Neither propranolol nor nitrate administration was discontinued for the study. No patient had clinical, electrocardiographic, or radiologic evidence of right ventricular hypertrophy, lung disease, congestive heart failure, or valvular heart disease.

Exercise protocol: An intravenous cannula was inserted just before the exercise test and a baseline 12-lead electrocardiogram was recorded with each patient in the supine and standing positions and during hyperventilation. Patients were then exercised on a treadmill according to the Bruce protocol[5] until fatigue or significant chest pain developed. Heart rate, blood pressure, and a 12-lead electrocardiogram were recorded every minute, and a V_5 lead was continuously monitored. A dose of 1.5 mCi of thallium-201 (New England Nuclear, North Billerica, Massachusetts) was injected intravenously at peak exercise and the patient was encouraged to continue exercising

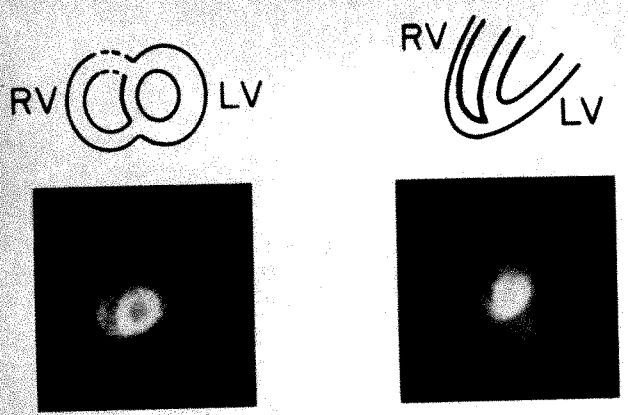

FIGURE 1. Initial 45° (**left**) and 70° (**right**) left anterior oblique (LAO) images in a patient without coronary artery disease, displaying typical RV thallium-201 activity. Above the images is a diagram illustrating the right (RV) and left ventricles (LV).

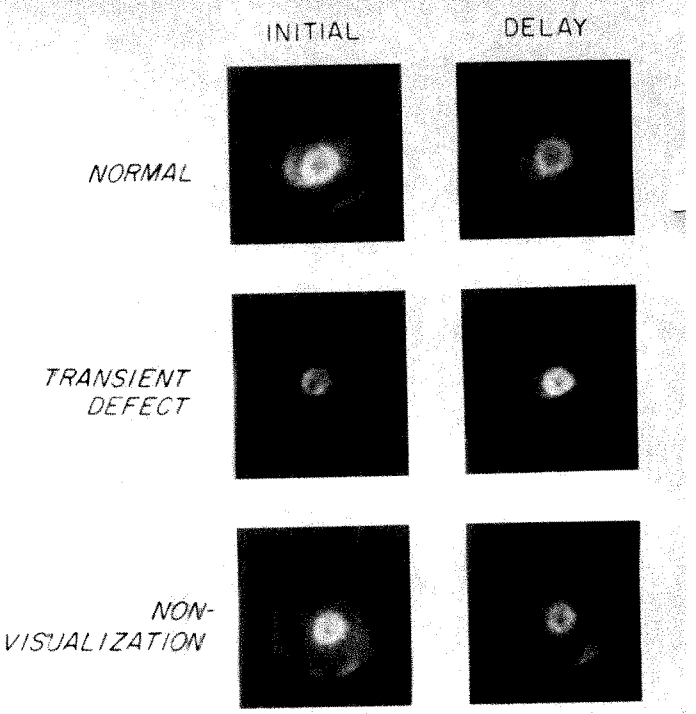

FIGURE 2. Representative examples of serial 45° left anterior oblique thallium-201 images, displaying normal activity, transient defect, and nonvisualization of the right ventricle.

for an additional 45 seconds. A positive ischemic electrocardiographic response was defined as S-T segment depression ≥1 mm both at the origin and 80 ms later.

Image acquisition: Imaging was performed with the patient supine using an Anger-type camera (Ohio Nuclear Series 420, Technicare, Solon, Ohio) equipped with a low energy all-purpose parallel hole collimator. Images were recorded using a window of 68 to 80 keV encompassing the mercury x-ray peak of thallium-201. Imaging was begun within 5 minutes of cessation of exercise. Image collections were performed in the anterior, 45° left anterior oblique, and 70° left anterior oblique views for 10 minutes each. Delayed views were obtained in 2 to 4 hours. Images were stored in a commercially available imaging computer system for analysis (MUGA-CART, Medical Data Systems, Ann Arbor, Michigan).

Imaging analysis: RV thallium-201 activity was analyzed in the left anterior oblique view which best separated the right from the left ventricle (Fig. 1). The RV appearance was graded by at least 2 independent observers in a blind manner without knowledge of the coronary angiographic results as follows: 0 (absent), 1 (reduced activity compared with that of the left ventricle, but clearly defined), or 2 (prominent, equal to the left ventricle in intensity). Half-grade scores were used to describe right ventricles that were either present but very faint and poorly defined (such as 0.5) or prominent but not quite equal to the left ventricle in intensity (such as 1.5). Differences in interpretation were resolved by consensus. Studies were shown on 2 occasions to allow determination of intraobserver agreement. When the right ventricle was initially graded 1.0 (clearly defined) or more, RV activity was termed "normal" (Fig. 2). When RV activity was initially graded 0 or 0.5 (not visualized or poorly defined) and increased to grade 1.0 (clearly defined) or better on the delayed view, the right ventricle was interpreted as demonstrating a "transient defect" (Fig. 2). When the right ventricle was graded 0 or 0.5 on both initial and delayed views, RV activity was interpreted as "nonvisualized" (Fig. 2). No right ventricle demonstrated initial activity of grade 1.0 that increased on the delayed view.

Interobserver agreement on RV interpretation was 92% for normal, 88% for transient defect, and 90% for nonvisualization. Intraobserver agreement on RV interpretation was 94% for normal, 88% for transient defect, and 90% for nonvisualization.

The serial left ventricular inferior wall thallium-201 distribution was analyzed in the anterior view and categorized as normal, transient defect, or persistent defect using averaged score criteria as previously described.[6] In addition, thallium-201 lung activity was qualitatively graded as 0 (normal), 1 (moderately increased), or 2 (markedly increased) using previously described criteria.[7]

Coronary angiographic data: All patients underwent selective coronary cineangiography. Coronary arteries were defined as demonstrating significant disease when luminal diameter was reduced ≥50% in 2 or more projections. Coronary dominance was noted: the posterior descending artery originated from the right coronary artery in 80 patients and from the left circumflex artery in 8. Proximal stenosis of the right coronary artery was defined as proximal to the origin of the acute marginal artery.

Patients were categorized by their coronary anatomy on the basis of the adequacy of blood supply to the right ventricle and left ventricular inferior wall. The 4 categories were based on the presence of stenosis in the right coronary or posterior descending artery system, or both, which indicated jeopardy of (1) the right ventricle and inferior wall, (2) the right ventricle alone, (3) the inferior wall alone, and (4) neither the right ventricle nor the inferior wall. The rationale for this division was derived from previous observations that the right ventricle is supplied primarily by the acute marginal branch of the right coronary artery and muscular branches proximal to this vessel, whereas the left ventricular inferior wall is supplied primarily by the posterior descending artery.[8–10] Thus, the coronary anatomy in the 4 groups was as follows (Table I): (1) proximal right coronary artery disease associated with significant stenosis proximal to the origin of the posterior descending artery (whether it originated from the right or left circumflex artery), (2) proximal right coronary artery disease without significant

TABLE I Grouping of Patients Based on Coronary Anatomy and Jeopardy to the Right Ventricle and Left Ventricular Inferior Wall

Group	Myocardium Jeopardized		Coronary Stenoses	
	Right Ventricle	Left Ventricular Inferior Wall	Proximal RCA	PDA
1	+	+	+	+
2	+	−	+	−*
3	−	+	−	+†
4	−	−	−	−

* Patients with a normal dominant left circumflex artery.
† Patients with distal right coronary disease or with normal right coronary and disease of a dominant left circumflex artery.
PDA = posterior descending artery; RCA = right coronary artery.

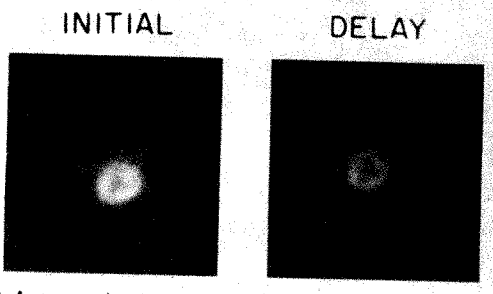

FIGURE 3. An example of nonvisualization of the lower half of the right ventricle in a patient with proximal right coronary artery disease.

stenosis proximal to the origin of the posterior descending artery (normal dominant left circumflex artery), (3) significant stenosis proximal to the origin of the posterior descending artery without proximal right coronary disease (distal disease of a dominant right coronary artery or disease of a dominant left circumflex artery with a normal nondominant right coronary artery), (4) neither proximal right coronary disease nor significant stenosis proximal to the origin of the posterior descending artery.

Collateral vessels to the right coronary artery from the left coronary artery were defined as good when on left coronary injection there was dense contralateral filling of the right coronary artery distal to a stenosis and defined as poor when there was no or only faint contralateral filling. Stenosis <90% of the right coronary artery was always associated with poor collateral vessels in both groups. Therefore, the relation of RV thallium distribution to collateral vessels was only evaluated in patients with right coronary artery stenosis ≥90%.

Statistical analysis: Frequency comparisons between patients were made using Fisher's test or the chi-square test. Mean data were expressed as mean ± 1 standard deviation and differences analyzed using one-way analysis of variance followed by a Neuman-Keuls multiple comparison test.

Results

RV appearance on thallium-201 myocardial images: Representative initial thallium-201 images displaying RV distribution in a patient without angiographic coronary artery disease are shown in Figure 1. The RV activity was generally best seen on the 45° left anterior oblique view. It appeared as a homogeneous semicircular ring from the apical to the basal portion of the septum. Frequently, the upper right ventricle adjacent to the basal septum was absent (Fig. 1), which probably corresponded to the point at which the RV free wall thins as it joins the pulmonary outflow tract. However, this area did not account for greater than a 10° portion of the entire right ventricle in normal subjects. The right ventricle usually appeared thinner and less bright than the septum, although in 2 patients without coronary disease the RV intensity was equal to that of the septum. In some patients, the right ventricle was best seen in the 70° left anterior oblique view, when it generally appeared curvilinear, extending from the apex toward the base. RV activity was not usually seen on the anterior view because of the superimposition of the left ventricle. The majority (80%) of patients, including all 15 patients without coronary artery disease, demonstrated normal right ventricular uptake of thallium-201.

Transient defects of the right ventricle were observed in 8 patients (9%) after exercise (Fig. 2). All RV transient defects involved both upper and lower halves, that is, the entire right ventricle. Nonvisualization of the right ventricle was observed in 10 patients (11%) after exercise. Two patients demonstrated nonvisualization isolated to the lower half of the right ventricle (Fig. 3). The remaining 8 patients had persistent nonvisualization of the entire right ventricle (Fig. 2).

Clinical findings: Table II shows clinical findings in relation to serial RV thallium-201 distribution after exercise. Of 88 patients, 17 (19%) had previous inferior myocardial infarction, but no patient had clinical evidence of a previous RV infarction.

There was no significant difference in age, sex, use of propranolol, incidence of previous inferior myocardial infarction, or incidence of exercise-induced inferior S-T segment depression in patients with normal right ventricular thallium activity, transient defects, or nonvisualization. The maximal exercise systolic blood

TABLE II Clinical Data and RV Thallium-201 Distribution

	RV Thallium-201 Distribution		
	Transient Defect (n = 8)	Nonvisualization (n = 10)	Normal (n = 70)
Age (yr)	52± 7	52 ± 12	53 ± 12
Sex (male/female)	8/0	9/1	61/9
Propranolol	7 (88%)	7 (70%)	38 (54%)
Previous inferior MI	4 (50%)	2 (20%)	11 (16%)
Exercise-induced inferior S-T depression	5 (63%)	5 (50%)	32 (46%)
Maximal systolic BP	135 ± 31*	109 ± 28†	147 ± 27
Maximal HR	107 ± 22†	126 ± 28†	137 ± 28
Maximal HR × BP (× 10^3)	14.6 ± 5.5†	19.0± 6.1	20.4 ± 6.6
≥85% predicted maximal HR	0 (0%)‡	3 (30%)	31 (44%)
Duration of exercise (min)	4.7 ± 2.6†	5.8± 2.5	5.6 ± 2.3

* $p < 0.01$, compared with normal. † $p < 0.001$, compared with normal. ‡ $p < 0.05$ compared with normal.
Group values are mean ± 1 standard deviation. BP = blood pressure; HR = heart rate; MI = myocardial infarction.

TABLE III Relation of Coronary Angiographic Findings to RV and Inferior Wall Thallium-201 Distribution After Exercise

Coronary Anatomy*	RV Thallium-201 Distribution			LV Inferior Wall Thallium-201 Distribution		
	Transient Defect (n = 8)	Nonvisualization (n = 10)	Normal (n = 70)	Transient Defect (n = 13)	Persistent Defect (n = 29)	Normal (n = 46)
RCA and PDA (n = 43)	7	8	28	9	21	13
RCA alone (n = 3)	1	1	1	1	0	2
PDA alone (n = 9)	0	0	9	2	4	3
Neither RCA nor PDA (n = 33)	0	1	32	1	4	28

* See Methods.
LV = left ventricular; PDA = posterior descending artery; RCA = right coronary artery.

pressure, maximal heart rate, maximal blood pressure-heart rate product, duration of exercise, and incidence of achieving 85% of the maximal predicted heart rate were all significantly lower in patients with right ventricular transient defects than in those with normal right ventricular images. In contrast, only maximal systolic blood pressure and maximal heart rate were significantly lower in patients with nonvisualized RV activity than in patients with normal RV thallium-201 distribution.

Coronary angiographic findings: The relation of RV thallium-201 distribution after exercise to coronary angiographic findings is demonstrated in Table III. Significant proximal right coronary artery disease was present in 8 of 8 (100%) patients with RV transient defects and 9 of 10 (90%) patients with nonvisualization of the right ventricle (including both patients with nonvisualization of only the lower half), compared with 29 of 70 (41%) patients with a normal RV appearance ($p < 0.005$ versus transient defect and nonvisualization). All 8 patients with RV transient defects had high grade (≥90%) stenosis of the proximal right coronary artery compared with that in 7 of 10 patients with nonvisualization (p = not significant) and 18 of 70 (26%) patients with normal RV distribution ($p < 0.001$).

Table III also shows the relation of left ventricular inferior wall thallium-201 distribution to coronary angiographic findings. Significant stenosis proximal to the origin of the posterior descending artery was present in 11 (85%) of 13 patients with transient defects of the inferior wall and 25 (86%) of 29 patients with persistent defects of the inferior wall compared with 16 (35%) of 46 patients with normal inferior wall appearance ($p < 0.001$) versus transient and persistent defects).

In 43 patients with both proximal right coronary disease and disease proximal to the origin of the posterior descending artery, the incidence of RV abnormality (15, or 35%) was significantly lower than that of inferior wall defects (30, or 70%) ($p < 0.001$). Of 3 patients with proximal right coronary disease without disease proximal to the origin of the posterior descending artery, 2 had RV abnormalities whereas 1 had an inferior wall defect. Of 9 patients with disease proximal to the origin of the posterior descending artery without proximal right coronary disease, all had a normal RV appearance whereas 6 had inferior defects. When there was neither proximal right coronary disease nor disease proximal to the origin of the posterior descending artery, the incidence of abnormal RV appearance (1 of 33, 3%) was not significantly different from that of inferior wall defects (5 of 33, 15%).

The incidence of left anterior descending artery disease was not significantly different in patients with normal RV appearance (60%), transient defects (75%), or nonvisualization (70%). In addition, left circumflex artery disease did not differ among the 3 groups. Similarly, the frequency of left ventricular thallium-201 defects other than inferior wall defects did not differ among the 3 patient groups.

The relation of collateral vessels to right ventricular thallium distribution is demonstrated in Table IV. Among patients with ≥90% stenosis of the proximal right coronary artery, normal RV appearance was more likely to occur when collateral vessels to the right coronary artery were graded as good (13 of 18, or 72%) than when they were graded as poor (5 of 15, or 33%) ($p < 0.05$).

The relation of degree of exercise (as assessed by heart rate response) to proximal right coronary disease and RV appearance is shown in Table V. RV thallium abnormalities in patients with proximal right coronary disease were more common when the heart rate response was less than 85% of maximal predicted values than when such a level of exercise was achieved ($p < 0.01$).

Relation to thallium-201 lung activity: The relation of RV thallium-201 uptake to thallium-201 lung

TABLE IV RV Thallium Distribution and Collateral Vessels Associated With ≥90% Stenosis of the Right Coronary Artery

Collateral Vessels	RV Thallium-201 Distribution					
	Transient Defect		Nonvisualization		Normal	
	n	%	n	%	n	%
Good	3	17	2	11	13	72
Poor	5	33	5	33	5	33

TABLE V Relation of Heart Rate Response to Exercise and Proximal Right Coronary Artery Disease to RV Thallium-201 Appearance

Proximal RCA Disease	≥85% Maximal Predicted Heart Rate	RV Thallium-201 Distribution: Transient Defect (n = 8)	Nonvisualization (n = 10)	Normal (n = 70)
Yes	Yes	0	3	12
Yes	No	8	6	17
No	Yes	0	0	19
No	No	0	1	22

RCA = right coronary artery.

TABLE VI Relation of RV Thallium-201 Distribution to Thallium-201 Lung Activity

Thallium-201 Lung Activity	RV Thallium-201 Distribution: Transient Defect (n = 8)	Nonvisualization (n = 10)	Normal (n = 70)
0 (normal)	4	3	25
1 (moderately increased)	3	7	27
2 (markedly increased)	1	0	17

activity is shown in Table VI. There was no significant difference in the distribution of RV thallium-201 patterns among the 3 groups of lung activity scores. However, despite proximal right coronary disease (false normal), normal right ventricular appearance was more likely to occur when lung activity was markedly increased (11 of 17) than when lung activity was normal (5 of 25) ($p < 0.01$).

Discussion

The association of left ventricular thallium myocardial defects with disease of coronary blood supply to the left ventricle is well accepted. However, few studies evaluate the diagnostic significance of the appearance of the right ventricle on thallium-201 myocardial imaging. Because of its lesser mass and blood supply[11,12] compared with those of the left ventricle, RV activity is usually not seen on resting thallium-201 studies.[13] Several reports have demonstrated that visualization of the right ventricle on resting studies may occur with right ventricular volume or pressure overload.[14,16] The right ventricle is usually well visualized in normal patients after exercise.[13] Significant stenosis of the coronary supply of the right ventricle might be expected to result in reduced perfusion of the right ventricle, reflected in reduced initial uptake in thallium. In this study, we found that such perfusion imaging abnormalities were relatively uncommon in the setting of proximal right coronary artery disease and were less frequent than left ventricular inferior wall defects (sensitivity 17 of 46, or 37 %, versus 31 of 46, or 67%, respectively). However, when they occurred, they were highly specific for proximal right coronary disease and in the case of right ventricular transient defects were always associated with high grade (≥90%) stenosis.

We have distinguished between transient RV defects and persistent nonvisualization of the right ventricle on serial myocardial imaging. Previous reports showed that with serial thallium-201 imaging, transient left ventricular defects suggest underperfused but viable myocardium, whereas persistent left ventricular defects suggest underperfused and scarred myocardium.[17,18] In the present study we were unable to determine whether the difference between transient and persistent defects applies to the right ventricle. Although segmental nonvisualization of the right ventricle limited to the lower half of the free wall was observed in 2 patients with proximal right coronary artery disease, no patient in the present series was known to have a RV myocardial infarction by clinical criteria and no pathologic (postmortem) data were available. In addition, although RV infarction has commonly been associated with left ventricular inferior myocardial infarction,[19,20] in our study the incidence of previous inferior infarction was not significantly different in patients with transient defects and those with persistently nonvisualized RV activity. Furthermore, radionuclide angiography, which might have assisted in detecting RV infarction, was not performed.

Potential diagnostic limitations of RV appearance: Poor visualization of the right ventricle on thallium-201 imaging may be caused by factors other than proximal right coronary disease. One factor may be inadequate exercise. RV activity is normally not discernible in studies at rest, and in a patient whose exercise is suboptimal, RV blood flow and thallium uptake may not increase adequately to allow visualization of the right ventricle. Such a study could result in interpretation of the right ventricle as "nonvisualized" even in the presence of a normal right coronary artery. In our study, heart rate response and blood pressure response to exercise was lower in patients with a nonvisualized compared with a normal RV appearance. In addition, abnormalities of RV appearance were more common among patients with submaximal heart rate response to exercise. However, such abnormalities occurred almost exclusively in patients with proximal right coronary artery disease. Of 23 patients without proximal right coronary disease who did not achieve adequate heart rate response, only 1 (4%) had nonvisualization of the right ventricle and none had a transient defect (Table IV). A second factor could include increased thallium-201 lung activity, which may result in nonvisualization of the right ventricle by reducing the myocardial-background ratio. In our study, however, increased lung activity was not associated with an increased incidence of nonvisualized segments or transient defects.

Conversely, there are also several factors that may result in normal RV appearance despite significant proximal right coronary disease. One factor would include any cause of increased RV work load or hypertrophy, such as chronic lung disease or pulmonary hy-

pertension of any cause, which is known to increase RV blood supply and thallium-201 uptake. A similar phenomenon may occur with transient increases in pulmonary vascular pressure secondary to exercise-induced left ventricular dysfunction, which is associated with increased thallium lung activity.[27] This possibility is suggested by our observation that there was a higher incidence of normal RV appearance in the presence of proximal right coronary disease in patients with markedly increased thallium-201 lung activity after exercise than in patients with normal lung activity. In addition, exercise may increase RV work and blood supply, and thus thallium-201 uptake to allow visualization of the right ventricle even in the presence of right coronary artery stenosis. This finding may explain why abnormalities of RV appearance in patients with proximal right coronary disease were less common among those who achieved 85% maximal predicted heart rate than in patients who failed to reach such a level of exercise (Table IV). Another factor influencing RV appearance in patients with proximal right coronary disease may be the status of collateral vessels. In our study, normal RV appearance with high grade proximal stenosis was more common when collateral vessels were good than when they were poor. Lastly, because RV uptake was generally less than left ventricular activity, even in normal patients, an abnormality was judged present only when the right ventricle was not clearly visualized on an initial image. Thus, proximal right coronary stenosis could cause reduced but still discernible RV uptake that is not qualitatively distinguishable from RV activity in normal patients. This is unlike left ventricular segmental scoring in which 1 wall is graded in relation to another and may account for the greater sensitivity of left ventricular inferior wall defects for proximal right coronary disease than RV abnormalities. Future quantitative analysis of RV activity may improve sensitivity for right coronary artery disease.

Diagnostic value of serial RV thallium-201 imaging: Despite potential limitations as outlined, our study showed that evaluation of RV appearance on serial thallium-201 myocardial imaging after exercise may provide useful information with respect to proximal right coronary artery disease: (1) transient defects of the right ventricle after exercise suggest high grade (≥90%) proximal stenosis of the right coronary artery; (2) nonvisualized RV activity after exercise also suggests the presence of significant (≥50%) proximal right coronary artery disease; (3) normal RV appearance, however, frequently occurs despite significant proximal right coronary artery disease and thus does not exclude such disease.

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Enhanced Transcardiac l-Norepinephrine Response During Cold Pressor Test in Obstructive Coronary Artery Disease

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An increase in cardiac sympathetic activity can enhance coronary vasomotor tone and lower the ventricular fibrillation threshold. We compared the transcardiac l-norepinephrine responses during cold pressor test of 20 patients with normal coronary arteries with those of 23 patients with obstructive coronary artery disease. Baseline hemodynamic data did not differ in the 2 patient groups except for left ventricular end-diastolic pressures; mean values (± standard deviation [SD]) were 10 ± 3.7 and 15 ± 4.5 mm Hg in patients with normal and abnormal coronary arteries ($p < 0.01$). Baseline l-norepinephrine contents averaged 295 ± 152 (normal coronary arteries) and 250 ± 134 pg/ml (coronary artery disease) in the arterial blood, and 273 ± 152 and 250 ± 115 pg/ml, respectively, in the coronary sinus blood. Hemodynamic responses during cold stimulus were similar in both groups. Also, cold pressor-induced increases in arterial and coronary sinus l-norepinephrine contents were balanced in patients with normal coronary arteries, averaging 19 ± 30 and 17 ± 37%, respectively. In patients with coronary artery disease, however, a 26 ± 58% increase in arterial l-norepinephrine contents was associated with a 58 ± 62% increase in coronary sinus l-norepinephrine contents ($p < 0.02$), suggesting myocardial l-norepinephrine net release. It is concluded that transcardiac l-norepinephrine responses during cold stimulus are enhanced in patients with obstructive coronary artery disease. This response to a relatively mild sympathetic stress, reproducible by a variety of analogous stressful situations during daily life, could present an increased risk for acute cardiac events.

Studies during the past decade have demonstrated that sympathetic nervous activity can play an important role in the regulation of coronary blood flow. It became apparent that alpha-adrenergic–mediated coronary vasoconstriction can compete with metabolically induced coronary vasodilatation, particularly in myocardial regions with decreased coronary reserve.[1–7]

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Recent studies have also emphasized that increased sympathetic nervous activity enhances ventricular irritability and lowers the threshold to ventricular fibrillation in the ischemic myocardium.[8–11] Because these observations suggest that increases in sympathetic nervous activity could place the patient with obstructive coronary artery disease at increased risk, we measured arterial and coronary sinus l-norepinephrine contents during relatively mild sympathetic stress in these patients and compared their response in transcardiac l-norepinephrine pattern with that in patients with normal coronary arteries. We selected cold pressor stimulation because it is probably similar to the level of sympathetic stress experienced frequently during daily life. Our data indicate that there is a substantially

greater increase in coronary sinus l-norepinephrine concentrations in patients with obstructive coronary artery disease than in those without disease.

Methods

Patient selection: Patients referred for heart catheterization for evaluation of angina pectoris or atypical chest pain were eligible for the study if they fulfilled the following criteria: (1) normal cardiac function as judged by clinical findings, chest x-ray, and history; (2) no medications except for a mild sedative or sublingual nitroglycerin (none 2 hours before the procedure); (3) no history or findings of hypertension (blood pressure: systolic ≥150 mm Hg, diastolic ≥95 mm Hg); (4) age under 70 years.

Procedure: Before heart catheterization, the patient was premedicated with diphenhydramine hydrochloride (Benadryl®), 50 mg intramuscularly. A #8 pigtail catheter was placed through the femoral artery into the ascending aorta and a #7 Goodale-Lubin catheter through the femoral vein into the midportion of the coronary sinus. The position of the catheter in the coronary sinus was confirmed by pressure wave form and blood oxygen tension (18 to 28 mm Hg). After placement of the catheters, the lights in the laboratory were dimmed, and conversation was kept at a minimum in an attempt to establish a "steady state." Five to 10 minutes later, left ventricular and aortic pressures were measured and aortic and coronary sinus blood samples obtained. Subsequently, the left hand of the patient, including the wrist, was immersed into a mixture of water and ice. At the onset of chest pain or of discomfort of the hand in the icewater or after 2.5 minutes of cold stimulus without symptoms, measurement of aortic pressure and sampling of aortic and coronary sinus blood were repeated. Routine left heart catheterization, including coronary arteriography, was then performed.

Blood was analyzed for l-norepinephrine and epinephrine concentrations and for oxygen tension. Ratios for myocardial l-norepinephrine uptake (extraction) or release (production were calculated by dividing the arterial-coronary sinus l-norepinephrine difference by the arterial content. Because plasma l-norepinephrine content is the net effect of neuronal l-norepinephrine release, reuptake, and metabolism,[12] the data are referred to as percentage of myocardial l-norepinephrine "net uptake" or "net release."

Determination of catecholamines: Contents of l-norepinephrine and epinephrine were measured in 1 ml of plasma with a high pressure liquid chromatograph (Waters 6000 A), using an LC-4 electrochemical detector.[13] The plasma was deproteinated, and after liquid solid extraction onto alumina, the catecholamines were eluted with 0.1 *M* $HCLO_4$. A 20 μl sample was injected into the high pressure liquid chromatograph and the individual catecholamines were separated on a μ-Bondapak C_{18} column, mobile phase (85:15 H_2O-methanol, 1% EDTA, 2 m*M* l-heptane sulfonic acid and 1% acetic acid, pH 3.8), flow rate 1 ml/min. Standards containing 200 pg/ml of l-norepinephrine and epinephrine were included along with each assay. In our laboratory, plasma catecholamine contents of 13 normal volunteers, obtained after 20 minutes of rest in the supine position, averaged 168 ± 41 (SD) pg/ml (l-norepinephrine) and 47 ± 17 pg/ml (epinephrine). The coefficient of variation of 13 duplicate determinations averaged 2.1 ± 1.5% (l-norepinephrine) and 4.5 ± 4.2% (epinephrine), respectively. The coefficients of variation of measurements, obtained at a 10-minute interval from patients before heart catheterization in the same environment as that of the patient studied, averaged 7.4 ± 5.0% and 6.8 ± 4.9% for l-norepinephrine in arterial and coronary sinus blood (n = 30) and 9.2 ± 5.8% for epinephrine in coronary sinus blood (n = 15).

Data analysis: The response to the cold pressor test within each study group was tested with a 2-tailed paired *t* test. The difference in responses between the 2 study groups was evaluated by analysis of variance with baseline values as covariates. A p value <0.05 was considered statistically significant.

Results

Patients: Twenty-three patients with normal coronary arteries, 16 male and 7 female, and 23 patients with abnormal coronary arteries, 17 male and 6 female, were

TABLE I Transcardiac Catecholamine Responses to Cold Pressor Test*

Measurement	Normal Coronary Arteries (n = 20) Control	Cold Pressor	P	Abnormal Coronary Arteries (n = 23) Control	Cold Pressor	P	Δ Normal Coronary Arteries	vs	Δ Abnormal Coronary Arteries	P
Heart rate (beats/min)	73 ± 15	80 ± 16	<0.001	76 ± 15	83 ± 22	<0.01	+6.5 ± 7.2		+6.6 ± 11	NS
Arterial pressure (mm Hg)										
Systolic	138 ± 20	168 ± 26	<0.001	146 ± 20	178 ±21	<0.001	+29 ± 17		+31 ± 15	NS
Diastolic	78 ± 11	95 ± 13	<0.001	80 ± 10	102 ± 11	<0.001	+17 ± 11		+21 ± 11	NS
Mean	101 ± 13	122 ± 21	<0.001	105 ± 15	132 ± 21	<0.001	+20 ± 16		+27 ± 18	NS
Double product (mm Hg × beats/min × 10^3)	10.3 ± 3.1	13.6 ± 4.0	<0.001	11.2 ± 2.9	14.6 ± 3.6	<0.001	+3.2 ± 2.2		+3.2 ± 1.5	NS
Left ventricular filing pressure (mm Hg)	10 ± 3.7	...	...	15 ± 4.5	...	...	...		...	...
NE content (pg/ml)										
Arterial	295 ± 152	339 ± 174	<0.01	250 ± 134	285 ± 134	NS	+44 ± 67		+34 ± 115	NS
Coronary sinus	273 ± 152	301 ± 170	NS	250 ± 115	387 ± 250	<0.002	+28 ± 76		+137 ± 182	<0.012
Myocardial NE net uptake or release (%)	7.5 ± 29	10 ± 16	NS	7.2 ± 29	34 ± 53	<0.01	+2.9 ± 25		−27 ± 48	<0.003
EPI content (pg/ml)										
Arterial	69 ± 32	76 ± 54	NS	70 ± 43	77 ± 42	NS	+6.5 ± 39		+6.9 ± 29	NS
Coronary sinus	56 ± 29	62 ± 38	NS	60 ± 36	85 ± 53	<0.02	+7.4 ± 21		+25 ± 44	NS

EPI = epinephrine; NE = l-norepinephrine; NS = not significant.
* Values are mean ± standard deviation.

studied. The ages averaged 47 and 54 years, respectively, ranging from 31 to 65 and 30 to 67 years. The electrocardiogram was normal in all but 1 of the patients with normal and in 10 of the 23 patients with abnormal coronary arteries. Of the patients with coronary artery disease, 7 had ≥70% obstruction of 1 major dominant coronary artery, 8 patients of 2, and 8 patients of 3 major arteries. One patient had 70% stenosis of the left main stem. The left ventriculogram was normal in all patients with normal coronary arteries and showed various forms of hypokinesia or akinesia in patients with disease in segments related to the obstructed coronary artery. During cold stimulus, chest pain developed in 7 of 23 patients with coronary artery disease and was associated with depression of the S-T segment in 4 and elevation in 3. Six patients complained of chest pain without electrocardiographic changes. Two of the 23 patients with normal coronary arteries had chest pain without demonstrating other abnormalities. In 3 patients with normal coronary arteries a vagovasal reflex developed after the baseline measurements. Their results are reported separately herein.

Data on patients with normal and abnormal coronary arteries: Baseline data of the 2 patient groups are shown in Table I (mean ± SD) and Figure 1. The heart rate averaged 73 ± 15 and 76 ± 15 beats/min and aortic pressure 138 ± 20/78 ± 11 and 146 ± 20/80 ± 10 mm Hg, respectively. Left ventricular end-diastolic pressure was the only hemodynamic measurement that differed in the 2 groups; mean values were 10 ± 3.7 and 15 ± 4.5 mm Hg ($p < 0.01$). Individual data of arterial l-norepinephrine contents and of the ratios of myocardial l-norepinephrine net uptake (extraction) or net release (production) are shown in Figure 1. In all but 8 patients plasma l-norepinephrine contents were below 350 pg/ml (twice the mean value for resting normal volunteers). Five of the 8 patients with higher plasma l-norepinephrine contents had a history of a "labile nervous system" and "anxiety." The myocardial l-norepinephrine ratios (Fig. 1) varied considerably. Two thirds of the patients with normal coronary arteries demonstrated myocardial l-norepinephrine net uptake, whereas more than half the patients with coronary artery disease showed myocardial l-norepinephrine net release.

Cold stimulus by insertion of the hand into ice cold water caused changes in hemodynanic function that were similar in patients with normal and those with abnormal coronary arteries (Table I, Fig. 2). Heart rate increased an average of 10 ± 11% and 9 ± 10%, respectively, systolic pressure 21 ± 12% and 22 ± 13%, diastolic pressure 23 ± 16% and 27 ± 16%, and double product 32 ± 26% and 29 ± 16%. Increases in arterial l-norepinephrine contents, like increases in hemodynamic measurements, were similar in the 2 groups: 19 ± 30% and 26 ± 58%, respectively. In contrast, cold pressor-induced increases in coronary sinus l-norepinephrine contents differed strikingly, averaging 17 ± 37% in patients with normal and 58 ± 62% in patients with abnormal coronary arteries. Accordingly, the myocardial l-norepinephrine ratios also responded differently to cold stimulus (Fig. 3). In the normal coronary artery group cold stimulus enhanced the percentage of both myocardial l-norepinephrine net uptake and release; the mean value of the ratios remained essentially un-

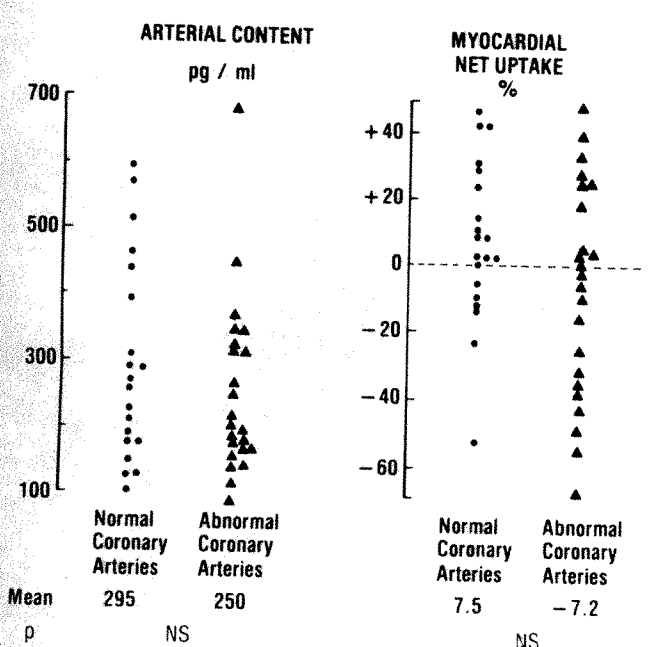

FIGURE 1. Baseline arterial l-norepinephrine contents and myocardial l-norepinephrine ratios. Arterial l-norepinephrine contents were similar in patients with normal and those with abnormal coronary arteries. Myocardial l-norepinephrine net uptake dominated in patients with normal coronary arteries, whereas l-norepinephrine net release dominated in those with abnormal coronary arteries. NS = not significant.

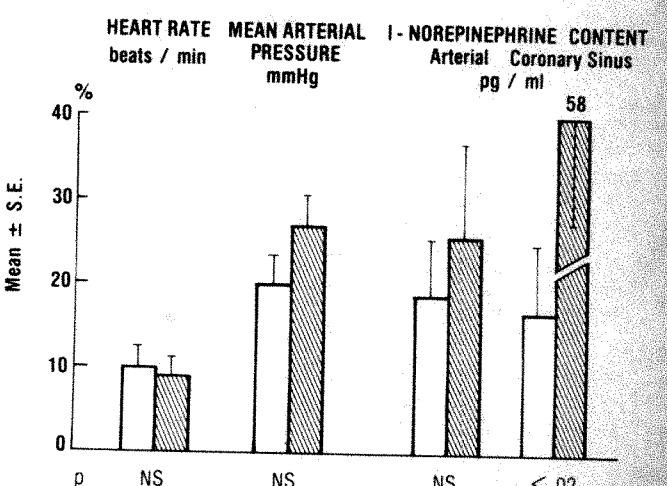

FIGURE 2. Cold pressor-induced changes in hemodynamics and plasma l-norepinephrine contents. Average increases in heart rate, mean arterial pressure, and arterial l-norepinephrine contents were similar in patients with normal (**open bars**) and those with abnormal (**hatched bars**) coronary arteries. In contrast, cold pressor-induced increases in coronary sinus l-norepinephrine contents were 3-fold higher in patients with coronary artery disease. NS = not significant.

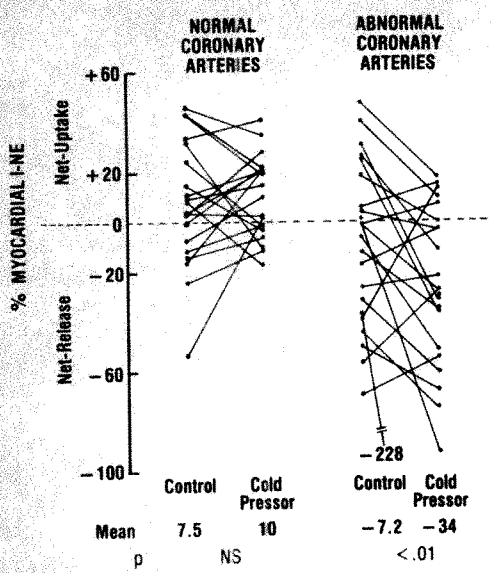

FIGURE 3. Ratios of myocardial l-norepinephrine (l-NE) net uptake (+) and l-norepinephrine net release (−). At control the majority of patients with normal coronary arteries demonstrated l-norepinephrine net uptake. The response to cold pressor varied; the mean value remained unchanged. In patients with abnormal coronary arteries myocardial l-norepinephrine net release dominated at control and was strikingly enhanced during cold stimulation. NS = not significant.

changed: 7.5 ± 29% and 10 ± 16%. In the abnormal coronary artery group, however, cold stimulus greatly enhanced the percentage of myocardial l-norepinephrine net release. Four patients had a decrease in myocardial net uptake and 14 patients had a shift from net uptake to release or enhanced l-norepinephrine net release; the mean value changed from −7.2 ± 29% to −34 ± 53% ($p < 0.01$). There was no relation between the increases in myocardial l-norepinephrine net release and the occurrence of chest pain and S-T segment changes. l-Norepinephrine net release was observed in patients with and those without findings of myocardial ischemia. Baseline arterial and coronary sinus epinephrine contents averaged about 50% above normal in both patient groups. The response to cold stimulus varied widely, and no statistically significant changes were observed.

In 3 patients with normal coronary arteries a vagovasal reflex developed after termination of the control study. The control data for arterial pressure and heart rate averaged 129 ± 8.8/85 ± 7.1 mm Hg and 98 ± 24 beats/min, respectively. During the sudden and unexpected vagovasal reflex, heart rate and arterial pressure were not recorded on paper but were observed either on the digital readout of the monitor or by blood pressure cuff. Restlessness and movement of the patient caused difficulties in obtaining the recordings. However, the heart rate decreased below 30 beats/min in all 3 patients and systolic blood pressure ranged from 40 to 60 mm Hg. After atropine, 1.0 mg intravenously, vital signs returned to normal; the mean values were 122 ± 2.8/76 ± 4.0 mm Hg and 85 ± 29 beats/min. The catecholamine response to the severe hypotensive stress during the vagovasal reflex was extensive. Plasma l-norepinephrine concentrations increased from 305 ± 100 pg/ml (control) to 973 ± 242 pg/ml in the aorta and from 264 ± 66 pg/ml (control) to 1,651 ± 353 pg/ml in the coronary sinus.

Discussion

The appearance of l-norepinephrine in blood represents a spillover from the synaptic cleft and is dependent on the level of neural stimulation, neuronal release and reuptake, blood flow, and extraneuronal metabolism.[12] Recent studies suggest that despite these limitations, plasma l-norepinephrine concentrations may be a better reflection of sympathetic neural activity than formerly believed, particularly when l-norepinephrine contents are measured across 1 specific organ. Yamaguchi et al[14] demonstrated a close relation among myocardial l-norepinephrine release, coronary blood flow, heart rate, and dP/dt during stellate ganglion stimulation in the dog; Cryer et al[15] showed in man that a prompt increase in heart rate and blood pressure after cigarette smoking was associated with a parallel increase in the l-norepinephrine contents of venous blood.

Transcardiac l-norepinephrine patterns have been studied under various conditions in man and in the experimental animal. The normal heart extracts l-norepinephrine under resting conditions.[16–20] l-Norepinephrine is released by the normal heart under conditions of substantial stress such as rapid cardiac pacing, handgrip exercise,[19–21] or stellate ganglion stimulation.[14] A vigorous noradrenergic response of the heart with a 5-fold increase in arterial and 10-fold increase in coronary sinus l-norepinephrine concentrations was observed by us in patients with normal coronary arteries and normal left ventricular function experiencing a vagovasal episode. Thus, the normal heart appears able to participate in the neurohumoral response to stress.

The ischemic heart, in contrast, releases l-norepinephrine at rest and this release may be further increased by the application of certain stresses. Handgrip[19–21] or ergometer exercise[22,23] leads to enhanced l-norepinephrine release in patients with coronary artery disease; reperfusion experiments after transient coronary occlusion in experimental animals[24–26] produce similar findings. Remarkably high concentrations of l-norepinephrine are found in coronary sinus blood in patients with acute myocardial infarction.[27]

The present study was designed to determine whether relatively mild stressful stimuli would evoke different responses in individuals with significantly obstructed coronary arteries compared with those with normal coronary arteries. Immersion of the hand in cold water—the classic cold pressor test—was selected as a stimulus that might produce a sympathetic response similar to responses experienced frequently during everyday life.

The transcardiac plasma l-norepinephrine patterns showed a major difference in the response to cold

pressor stimulation in the 2 patient populations. The mild, balanced increases in arterial and coronary sinus l-norepinephrine concentrations in the individuals with normal coronary arteries and normal cardiac function suggest a generalized sympathetic response to afferent stimuli from the periphery,[28–30] initiated from the chilled limb. A similar mild increase in arterial l-norepinephrine concentrations, but a 3-fold increase in coronary sinus concentration in those patients with obstructive coronary artery disease suggest an exaggerated response of the heart. This local cardiac response could reflect a cardiocardiac reflex as observed by Brown, Malliani, and their associates.[31–33] Transient coronary occlusion in the cat resulted in increased discharge of sympathetic afferent and preganglionic nerves associated with an increase in cardiac sympathetic activity. Changes in concentrations of hydrogen ions and potassium, hypoxia, and mechanical factors, including myocardial dysfunction,[32–35] have been suggested as mechanisms for this reflex. In the present study ischemia and impaired left ventricular function, triggered by cold stimulus, could have evoked a cardiocardiac reflex. More than half the patients with significantly obstructed coronary arteries exhibited myocardial ischemia during cold stimulus in the form of S-T segment depression, S-T segment elevation, or angina pectoris, or all 3. Left ventricular end-diastolic pressures were higher in patients with abnormal coronary arteries than in those with normal vessels so that cold stimulus-induced increases in blood pressure could have further impaired left ventricular function.[7] This possibility is consistent with the observation in patients with coronary artery disease that myocardial l-norepinephrine release during handgrip exercise was negatively related to ventricular ejection fraction[20,21] and that coronary sinus l-norepinephrine concentrations were positively related to left ventricular end-diastolic pressures.[36]

Factors other than an increase in myocardial release of l-norepinephrine might have contributed to the increase in coronary sinus l-norepinephrine concentrations during cold stimulus. l-Norepinephrine reuptake was shown to be impaired by myocardial ischemia.[37–39] In addition, cold stimulus-induced decreases of flow in diseased coronary arteries[6,7] could have exaggerated the increase in coronary sinus l-norepinephrine concentrations. The design of the study does not allow differentiation among the various mechanisms. We elected not to measure coronary blood flow in this study. Cold stimulus-triggered changes in total coronary blood flow would have been of limited value in the presence of inhomogeneity of perfusion. A decrease in venous efflux from the diseased myocardial compartment would lead to underrepresentation of abnormalities in total coronary sinus blood. Results of regional flow measurements, however, without those of regional l-norepinephrine determinations would have been difficult to interpret.

The increases in coronary sinus l-norepinephrine concentrations observed in our patients with obstructive coronary artery disease during the relatively mild sympathetic stress of cold stimulus probably occur numerous times during daily routine. Repetitive and cumulative bursts of neurotransmitter could decrease regional coronary perfusion,[3–6] increase local oxygen demand,[40] change substrate availability,[41,42] and alter the electrical properties of the myocardium.[8–11] The potential hazard of increased myocardial l-norepinephrine concentrations supports the suggestion that reducing overall sympathetic tone by antiadrenergic agents might be a useful therapeutic intervention in patients with ischemic heart disease.

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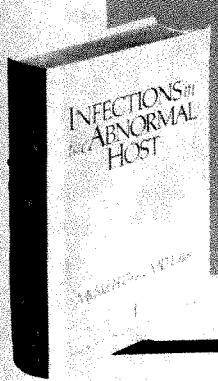

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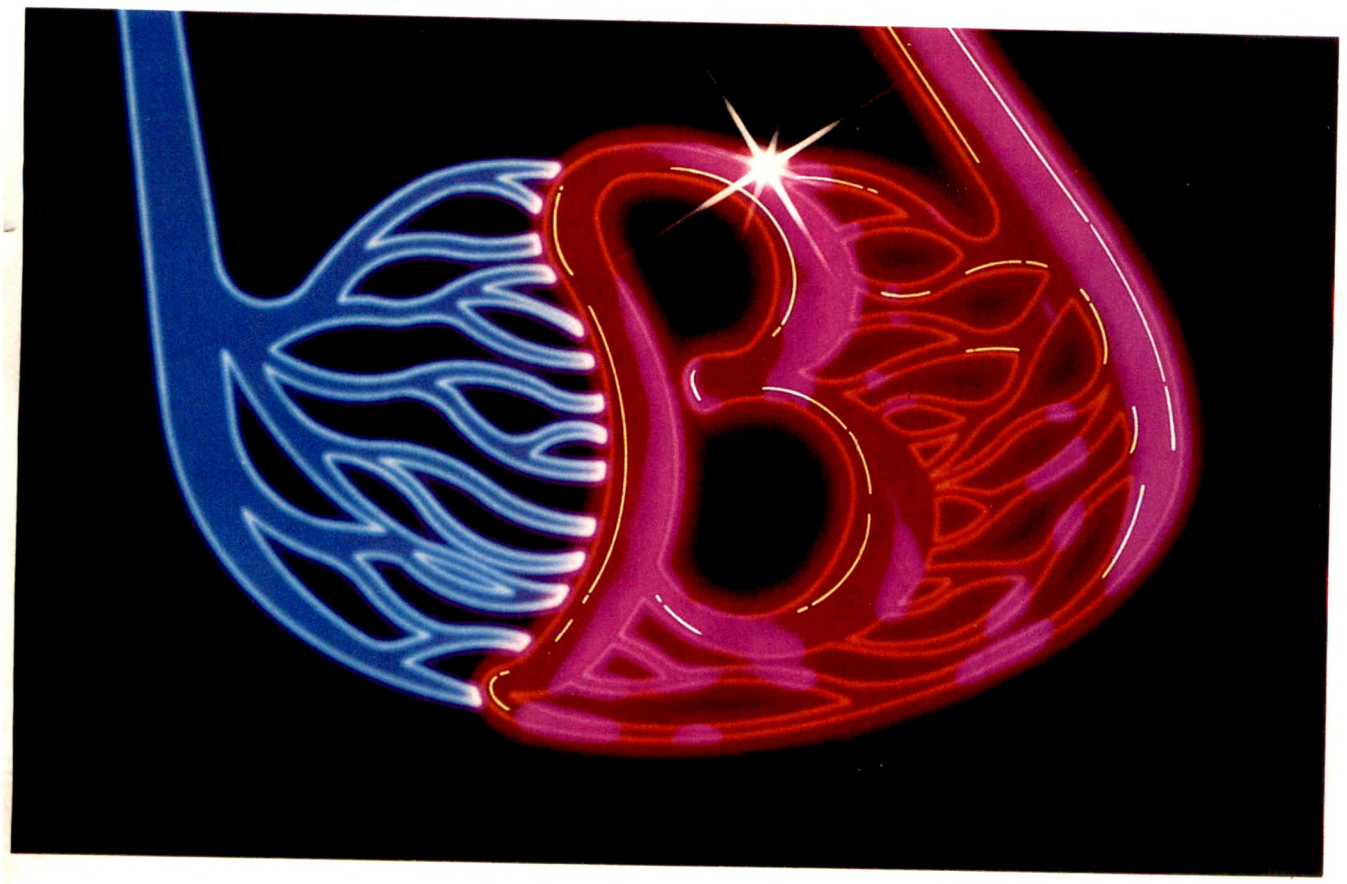

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4. None of the above

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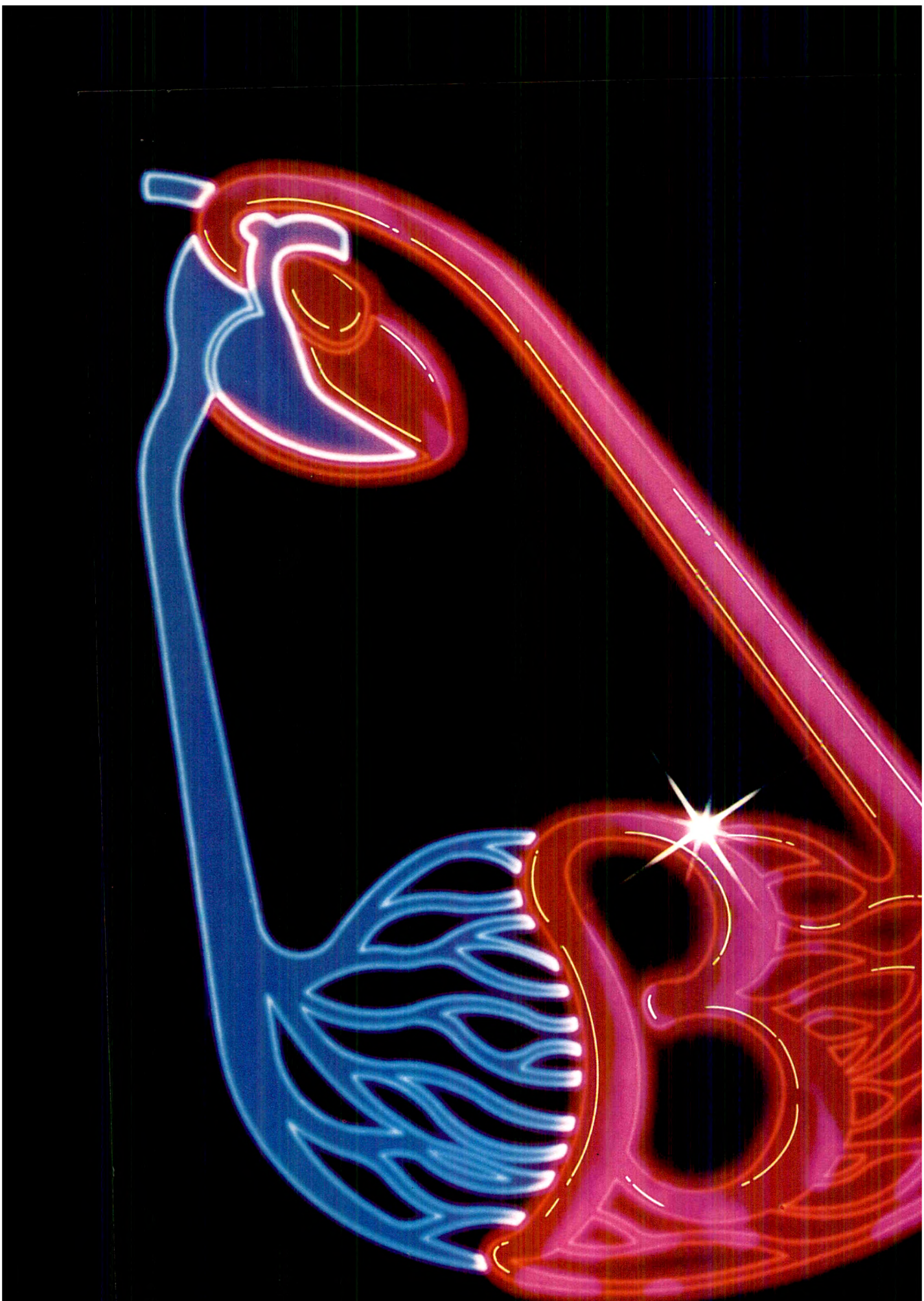


Introducing:

Visken® (pindolol)

the only beta blocker that reduces blood pressure and total peripheral resistance

Here's the difference:

Blood pressure

Blood pressure equals cardiac output times total peripheral resistance.

$$bp = co \times tpr$$

Visken (pindolol)

Visken (pindolol) is the only beta blocker that reduces blood pressure while maintaining resting cardiac output and reducing total peripheral resistance during long-term therapy.

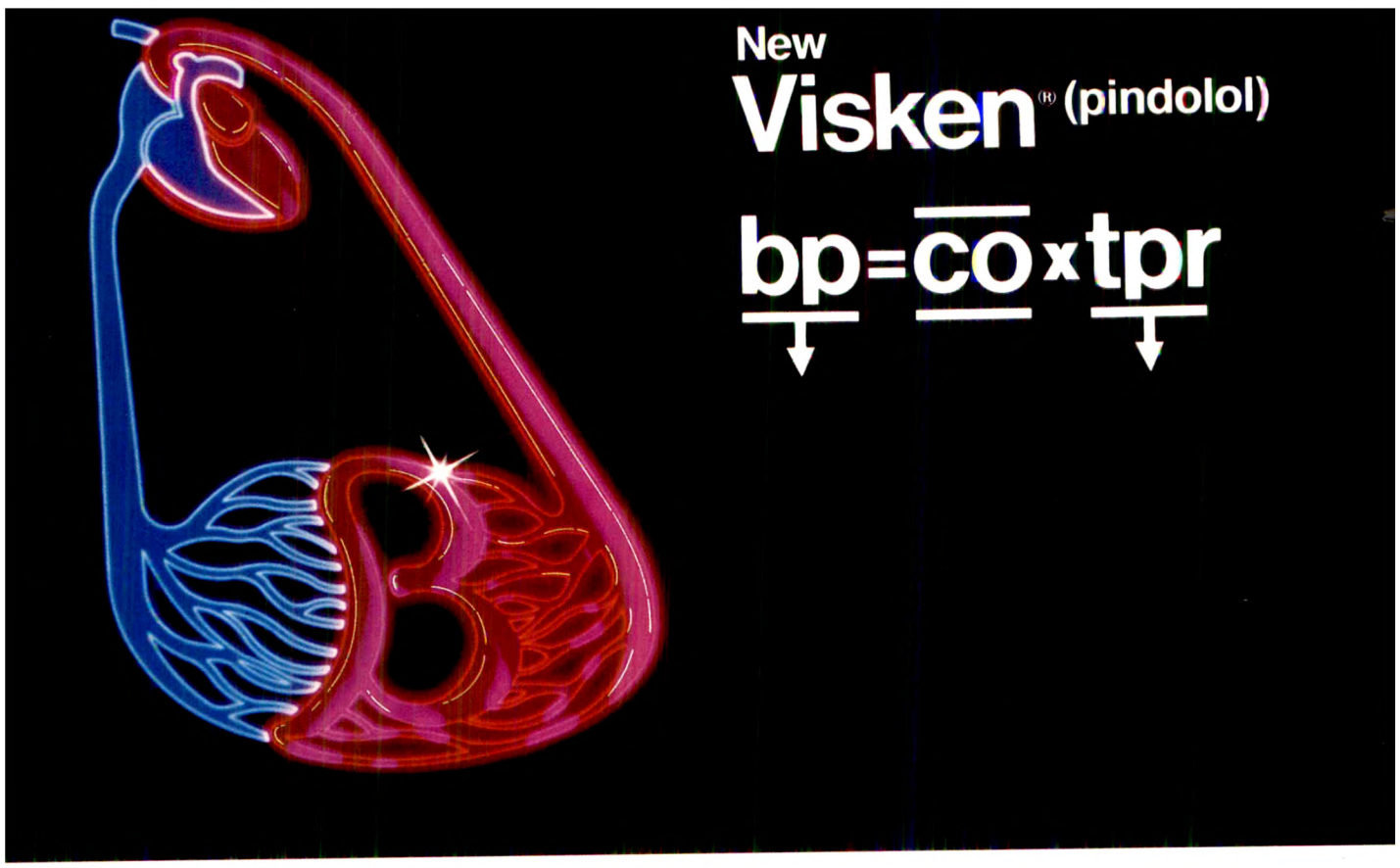
$$\underline{bp} = \underline{\overline{co}} \times \underline{tpr}$$

All other beta blockers

All other beta blockers reduce blood pressure, and reduce cardiac output with an initial reflex rise in total peripheral resistance and a subsequent return to baseline in many cases.

$$\underline{bp} = \underline{co} \times \overline{tpr}$$

Please see last page of this advertisement for brief summary of prescribing information.



Here's the result:

Reduced blood pressure

U.S. studies at 29 major medical centers[1] have shown that Visken (pindolol) is an effective antihypertensive. It is as effective as propranolol in normalizing blood pressure (dbp≤90 mmHg) when used alone. It is also effective when used in combination with a diuretic.

This antihypertensive effectiveness is supported by 13 years of clinical use throughout the world. In fact, Visken (pindolol) is the #2 beta blocker in the rest of the world.

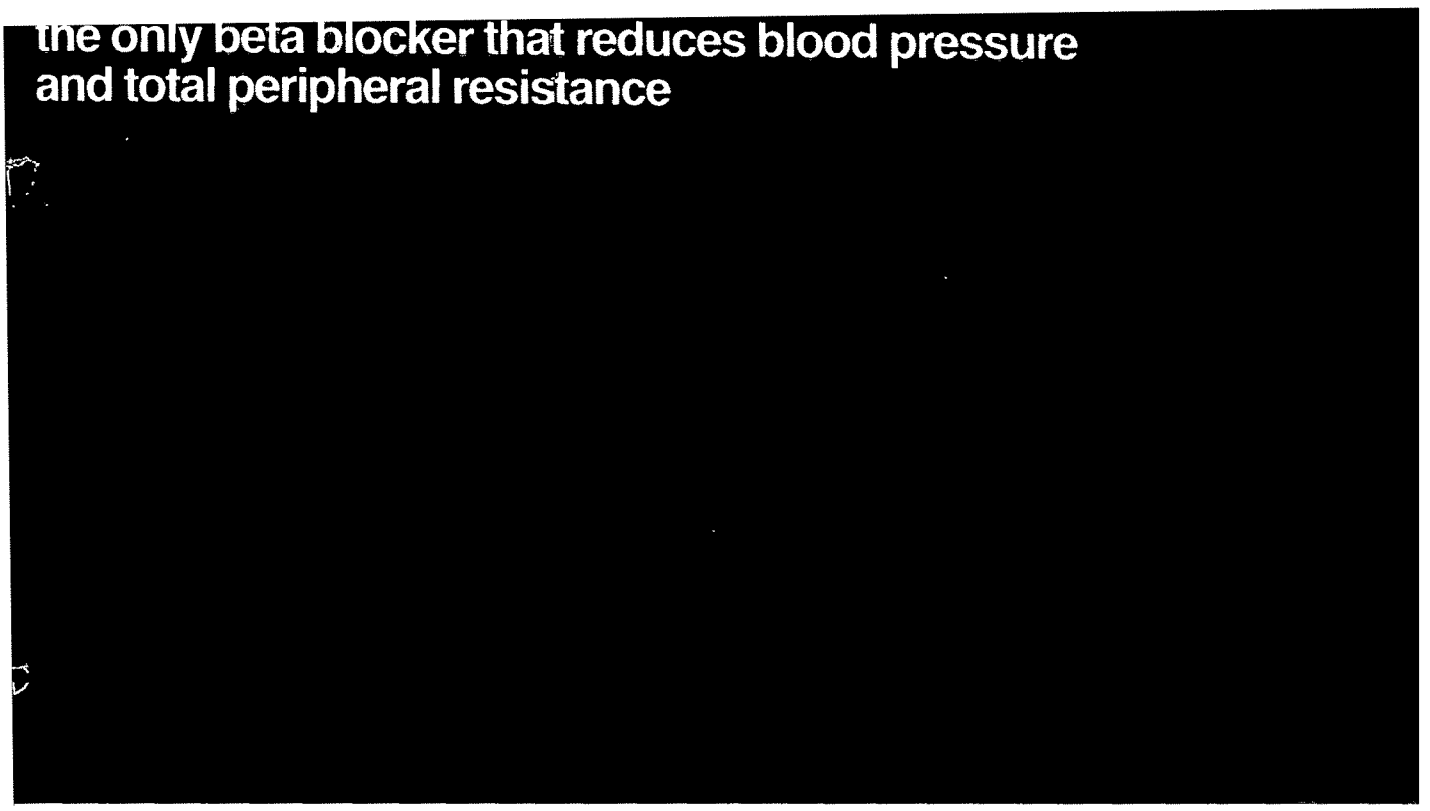
Reduced peripheral resistance

Studies of 178 patients treated with Visken (pindolol) for at least two weeks have shown that Visken therapy reduces total peripheral resistance.[1]

Reduction of exercise-induced tachycardia

Like other beta blockers, Visken (pindolol) blocks stimulation by catecholamines to reduce exercise-induced increases in systolic blood pressure and heart rate.

the only beta blocker that reduces blood pressure and total peripheral resistance



Here's the importance:

Visken® (pindolol) makes hemodynamic sense in the treatment of hypertension

Visken (pindolol) treats the basic abnormality of hypertension: increased peripheral resistance.

Visken (pindolol) reduces blood pressure with little effect on resting cardiac output

Unlike other beta blockers, Visken (pindolol) has little effect on resting cardiac output during long-term therapy. The clinical significance of this observation has not been evaluated.

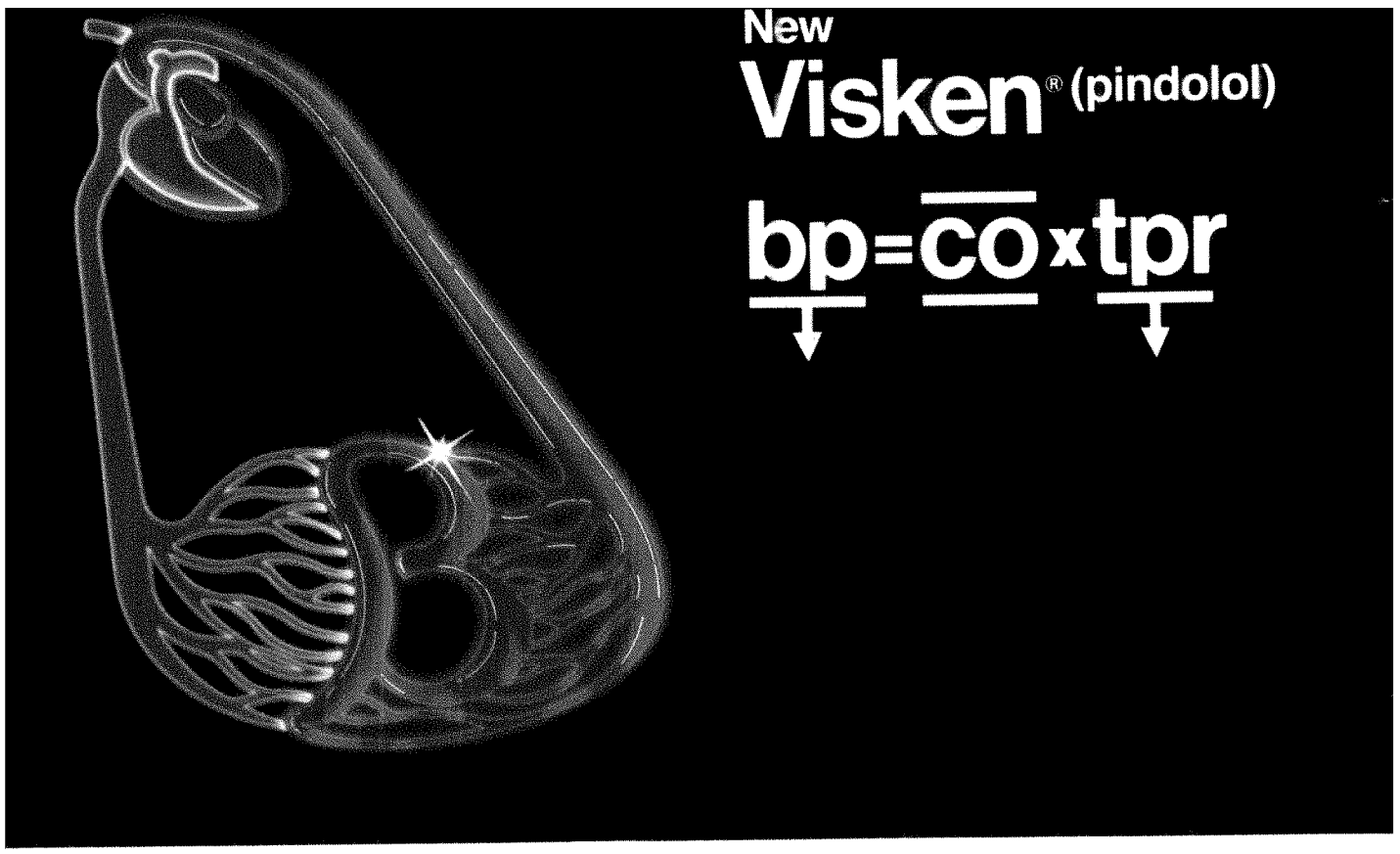
Visken (pindolol) reduces blood pressure with little effect on resting heart rate

Visken (pindolol) produces minimal changes in resting heart rate. Average reduction: 4-8 beats/minute. Minimal effect on resting heart rate results in low potential for bradycardia.

Visken (pindolol) maintains renal blood flow

Visken (pindolol) reduces supine and standing blood pressure while maintaining effective renal plasma flow and glomerular filtration rates.[2]

See last page of this advertisement for brief summary of prescribing information.



Here's what you can expect:

Reduced total peripheral resistance

Minimal effect on resting cardiac output

Minimal effect on resting heart rate

Minimal effect on renal blood flow

Favorable side effect profile*

Low incidence of bradycardia

Low incidence of cold extremities

* Visken (pindolol) is contraindicated in:

1) bronchial asthma
2) overt cardiac failure
3) cardiogenic shock
4) second- and third-degree heart block
5) severe bradycardia

Prescribing information:

Available in 5 mg and 10 mg tablets

Convenient bid dosage

Dosage should be titrated on an individual basis. Many patients respond to 10-30 mg a day in divided doses.

References:

Data on file, Sandoz Pharmaceuticals.
Alcox CS, Lewis PS, Peart WS, et al: Renal function, body fluid volumes, renin, aldosterone, and noradrenaline during treatment of hypertension with pindolol. *Cardiovasc Pharmacol* 3:598–611, 1981.

Please see last page of this advertisement for brief summary of prescribing information.

New Visken® (pindolol)

Before prescribing or administering, see package circular for full product information. The following is a brief summary.

INDICATIONS AND USAGE
Visken (pindolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide type diuretic.

CONTRAINDICATIONS
Visken (pindolol) is contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia; (see Warnings).

WARNINGS
Cardiac Failure: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients Without A History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers: Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of β_2 receptors.

Major Surgery: Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken® (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

PRECAUTIONS
Impaired Renal or Hepatic Function: Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

Information for Patients: Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

Pregnancy—Category B: Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

CLINICAL LABORATORY
Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

ADVERSE REACTIONS
Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

Body System/ Adverse Reaction	Total (Volunteered and Elicited) Visken (pindolol) (N = 322) %	Active Controls* (N = 188) %	Placebo (N = 78) %
Central Nervous System			
Anxiety	4	<1	1
Bizarre or Many Dreams	8	3	8
Dizziness	17	23	8
Fatigue	15	19	12
Hallucinations	1	0	0
Insomnia	19	8	12
Lethargy	3	6	4
Nervousness	11	5	9
Weakness	7	5	4
Autonomic Nervous System			
Paresthesia	5	2	8
Visual Disturbances	4	3	4
Body System/ Adverse Reaction	Total (Volunteered and Elicited) Visken (pindolol) (N = 322) %	Active Controls* (N = 188) %	Placebo (N = 78) %
Cardiovascular			
Dyspnea	9	8	9
Edema	11	9	3
Heart Failure	2	<1	0
Palpitations	2	2	0
Weight Gain	3	5	0
Musculo-Skeletal			
Chest Pain	5	3	5
Joint Pain	11	6	8
Muscle Cramps	8	2	0
Muscle Pain	12	12	9
Gastrointestinal			
Abdominal Discomfort	7	7	5
Nausea	7	4	1
Skin			
Pruritus	2	<1	0
Rash	2	3	3

*Active Controls: Patients received either propranolol, α-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

The following selected (potentially important) adverse reactions were seen in 2% or fewer patients and their relationship to Visken (pindolol) is uncertain. AUTONOMIC NERVOUS SYSTEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities, heart block, hypotension, syncope, tachycardia; GASTROINTESTINAL: diarrhea, vomiting. RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

POTENTIAL ADVERSE EFFECTS
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of Visken (pindolol).

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block. See CONTRAINDICATIONS.

Allergic: Erythematous rash; fever combined with chills and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic and nonthrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis; ischemic colitis.

Miscellaneous: Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with Visken (pindolol) during investigational use and extensive foreign experience amounting to over 4 million patient-years.

OVERDOSAGE
No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of Visken (pindolol), the following general measures should be employed as appropriate in addition to gastric lavage:

Excessive Bradycardia: administer atropine; if there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure: digitalize the patient and/or administer diuretic. It has been reported that glucagon may be useful in this situation.

Hypotension: administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pressure. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm: administer a beta$_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of Visken (pindolol) by a hypertensive patient. Blood pressure increased and heart rate was ≥80 beat/min. Recovery was uneventful. In another case 250 mg of Visken (pindolol) was taken with 150 mg diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

DOSAGE AND ADMINISTRATION
The dosage of Visken (pindolol) should be individualized. The recommended initial dose of Visken (pindolol) is 5 mg b.i.d. alone or in combination with other antihypertensive agents. Many patients will respond to 15 mg per day (5 mg t.i.d.). The antihypertensive response usually occurs within the first week of treatment. If a satisfactory reduction in blood pressure does not occur within 2-3 weeks, the dose may be adjusted in increments of 10 mg per day at 2-3 week intervals up to a maximum of 60 mg per day.

HOW SUPPLIED
White, round, scored tablets: 5 mg and 10 mg, packaged in bottles of 100. 5 mg tablets embossed "VISKEN 5" on one side, and "78-111" and scored on other side (NDC 0078-0111-05). 10 mg tablets embossed "VISKEN 10" on one side, and "78-73" and scored on other side (NDC 0078-0073-05).

[VIS-Z2 9-1-8]

Pharmaceutical Division
SANDOZ, INC.
East Hanover, NJ 07936

VIS-11

The QT $>QS_2$ Syndrome: A New Mortality Risk Indicator in Coronary Artery Disease

HARISIOS BOUDOULAS, MD, YOUNG HO SOHN, MD, WILLIAM O'NEILL, MD, ROGER BROWN, BS, and ARNOLD M. WEISSLER, MD

In the normal population the duration of electrical systole (QT) is shorter (mean −26 ± 13 ms, 1 standard deviation) than that of electromechanical systole (QS_2), which it closely parallels throughout the range of resting heart rate. This close association prompted the hypothesis that the duration of QT may be more closely linked physiologically to QS_2 than to the heart rate and hence may provide a more potent prognostic indicator than the relation of QT to heart rate. The present study was designed to test this hypothesis. One hundred stable patients 14 months after myocardial infarction were followed up an average of 43 months. Twenty patients had prolongation of QT relative to QS_2 (QT $>QS_2$) and 13 patients had long QT corrected for heart rate (QTc). There were 20 deaths (16 sudden). The cumulative 5 year survival rate was 35% in patients with QT $>QS_2$ and 91% in patients with QT $\leq QS_2$ ($p < 0.001$). There was no significant difference in survival in patients with long QTc compared with patients with normal QTc (69 versus 82%). Univariate and multivariate analysis for the association of QT $>QS_2$ with known risk factors, clinical descriptors, drug therapy, systolic time intervals (preejection period/left ventricular ejection time), and frequency of 1, 2, and 3 vessel coronary occlusive artery disease revealed that only the presence of abnormal preejection period/left ventricular ejection time added significantly to the presence of QT $>QS_2$ in stratifying 5-year survival into high and low risk groups. Thus, in patients with coronary artery disease, the presence of QT $>QS_2$ provides a new risk indicator that is more potent than QT corrected for heart rate.

Prolongation of electrical systole (QT) is associated with a high incidence of ventricular arrhythmia and sudden death in patients with and without coronary artery disease.[1–5] Traditionally, the heart rate is employed for correcting the duration of electrical systole and hence for identifying patients with prolongation of the QT interval.[6–8] Recent studies from our laboratory have demonstrated that the duration of the QT interval in normal persons is consistently shorter and closely parallels the duration of electromechanical systole (QS_2) throughout the normal range of resting heart rate.[9,10]

From the Department of Medicine, Wayne State University, and Harper-Grace Hospitals, Detroit, Michigan, and the Cardiovascular Center, Veterans Administration Medical Center, Allen Park, Michigan. This work was supported in part by a grant from the Veterans Administration Research Advisory Group and Harper-Grace Hospitals, Allen Park and Detroit, Michigan. Manuscript received February 9, 1982; revised manuscript received June 1, 1982, accepted June 16, 1982.

Address for reprints: Harisios Boudoulas, MD, Division of Cardiology, Veterans Administration Medical Center, Allen Park, Michigan 48101.

The close association between the duration of the QT and QS_2 intervals prompted the hypothesis that QT may be more closely linked physiologically to the duration of electromechanical systole than to heart rate. The relation of the QT to the QS_2 interval may therefore provide a more pertinent reference standard for defining lengthening of the QT than the traditional correction for heart rate. If this hypothesis is correct, the relation of the QT interval to QS_2 should provide a more sensitive measure of QT prolongation and hence be a more potent prognostic indicator than the relation of the QT interval to heart rate. The present study was undertaken to test this hypothesis in patients with established coronary artery disease.

Methods

One hundred consecutive patients with stable coronary artery disease after previous myocardial infarction who were admitted for coronary arteriography were selected as subjects for this study between January 1974 and December 1977. The

reference myocardial infarction occurred an average of 14 months (standard deviation [SD] 2 months) before determination of the duration of electrical and electromechanical systole. Average follow-up time was 43 months (standard deviation 18 months), with a minimal follow-up period of 24 months. Patients with valvular heart disease, left intraventricular conduction defect, recent myocardial infarction (<3 months), and noncardiac diseases that might independently affect survival or did not allow clear detection of the temporal landmarks for measuring the pertinent intervals were excluded before selection of the patients for prospective study.

Noninvasive determinations were performed within 48 hours of diagnostic coronary arteriography. Noninvasive measures were obtained with the patients resting in the supine position and measurements were made without knowledge of the arteriographic observations. No patient in this study experienced typical angina pectoris or precordial discomfort during recording of the nonivasive measures.

The duration of electrical systole (QT) and that of electromechanical systole (QS_2) were measured from a simultaneously recorded phonocardiogram and electrocardiogram at a paper speed of 100 mm/s. The standard electrocardiographic lead best delineating the onset of QRS and a clear inscription of the T wave was selected for measurement of the QT interval. The QT interval was measured from the beginning of the Q wave to the termination of the T wave at the point of its merger with the T-P segment.[10,11] When the end of the T wave was not precisely delineated, its termination was taken as the point where the line of most rapid descent of the T wave transected the baseline between the T wave and the upstroke of the subsequent P wave.[11] When a T wave <3 mm was not apparent and a U wave interfered with the definition of the T wave, the patient was not entered in the study. A microphone (EFM contact microphone, frequency range 100 to 500 H was placed over the second left intercostal space in the parasternal area so that the aortic and pulmonary components of the second sound could be clearly distinguished. The QS_2 interval was measured from the onset of ventricular depolarization as delineated in a sharp Q wave, on a standard lead, to the first high frequency vibration of the aortic component of the second heart sound. The aortic component of the second heart sound was identified by observation of the normal respiratory pattern in the components of the second heart sound and by their temporal relation to the incisural notch on a simultaneously recorded carotid arterial pulse tracing. The aortic component of the second heart sound was taken as those high frequency vibrations that consistently preceded the incisural notch throughout the respiratory cycle. The measurements were obtained from at least 10 consecutive cardiac cycles which were averaged to obtain the mean QS_2 and QT. The QT minus the QS_2 ($QT - QS_2$) for each patient was calculated from this mean value. Because there is no temporal delay in recording the QT and QS_2 intervals, the $QT - QS_2$ can be measured alternatively as the interval from the end of the T wave to the onset of the aortic component of the second heart. All temporal measurements were expressed in milliseconds.

Among 50 normal subjects the QT interval was consistently shorter than the simultaneously measured QS_2 interval. The $QT - QS_2$ followed a Gaussian distribution with a mean of -26 ms ± 13 (1 SD). Lengthening of the QT relative to the QS_2 by 2 SD above the mean for the normal population was defined as abnormal lengthening of the QT relative to the QS_2 ($QT > QS_2$). Hence, any value of $QT - QS_2 > 0$ was considered abnormal. The patients were divided into 2 groups: those with a normal QT relative to QS_2 ($QT \leq QS_2$, n = 80) and those with a lengthened QT relative to QS_2 ($QT > QS_2$, n = 20). The QT was corrected for heart rate (QTc) employing the conventional Bazzett equation, $QTc = QT\sqrt{RR}$. The normal QTc averages 0.39 for male subjects and 0.415 for female subjects.[6] The range of normal about the mean QTc for each sex is the mean value ±0.04 as defined by Bazzett. Hence, any value of QTc >0.43 in the male or >0.455 in the female was considered abnormal. For each patient the QT was calculated as the mean of measurements made on the same consecutive beats as those used to calculate the QS_2. Four additional corrections based on various equations relating heart rate and QT interval were employed in detecting QT prolongation.[7,9,12,13]

To test the influence of electrocardiographic lead-to-lead variation on the $QT - QS_2$, the intervals were measured in 7 normal control subjects for 12 simultaneously recorded electrocardiographic leads. Only leads demonstrating clear delineation of the termination of the T wave were employed in the analysis. No significant lead-to-lead variation in $QT - QS_2$ was present (mean variation irrespective of sign 2.4 ms, SD 3 ms for 7 subjects). In calculating the interval $QT - QS_2$, the QRS duration is subtracted (QRS is a constant in both the QT and QS_2 intervals). Therefore, the duration of the ST-T component of the QT interval is the critical determinant of variations in the QT relative to QS_2.

In 5 patients with $QT > QS_2$, $QT - QS_2$ measurements were performed on more than 1 occasion at 1 month intervals. In each patient, consistent prolongation of QT relative to QS_2 was demonstrated on the repeated determinations.

Systolic time intervals were measured as previously described in our laboratory.[14,15] The QS_2 was corrected for heart rate (QS_2I) according to previously published linear regression data ($QS_2I = QS_2 + 2.1$ heart rate for male subjects and $QS_2I = QS_2 + 2.0$ heart rate for female subjects).[15] QS_2I followed a Gaussian distribution in normal subjects. The normal range of QS_2I was hence considered to be in the 2 standard deviation range. By this definition a QS_2I less than 518 ms for male subjects and less than 520 ms for female subjects was considered abnormally abbreviated. The ratio of the preejection period (PEP) to the left ventricular ejection time (LVET) was employed in defining left ventricular performance. In previous studies, this measure has proved as accurate an expression of left ventricular global performance as the left ventricular ejection fraction, determined by contrast ventriculography, in patients with coronary artery disease.[16–18] The normal PEP/LVET is 0.34 ± 0.04 (1 SD). A PEP/LVET of 0.42 was considered the upper (2 SD) limit of normal for both sexes.

Selective coronary cinearteriography was performed in all patients employing the Sones or Judkins technique. The degree of coronary arterial narrowing was assessed without knowledge of other invasive or noninvasive data by 2 of us who reached consensus as to the number of arteries involved with ≥70% luminal area narrowing (≥50% diameter narrowing).

Cumulative 5-year survival curves were calculated for patient groups divided according to (1) presence or absence of $QT > QS_2$, (2) presence or absence of QTc prolongation, and (3) presence or absence of QS_2I shortening. Because left ventricular performance is a major independent determinant of prognosis in patients with coronary artery disease, patients with and without $QT > QS_2$ were further subdivided into those with normal left ventricular performance (PEP/LVET ≤0.42) and those with abnormal left ventricular performance (PEP/LVET >0.42). In addition, the extent of arterial occlusive disease was compared for patients subgrouped according to the presence or absence of $QT > QS_2$. The cause of death in each patient was determined by interview with close

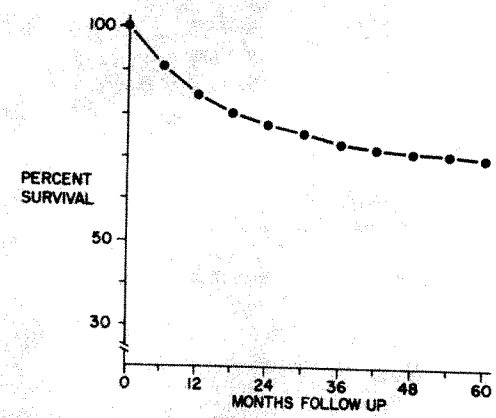


FIGURE 1. Cumulative 5-year survival rate after QT and QS_2 determination for the entire series (100 patients).

relatives and physicians and review of hospital charts. Sudden death was considered to be death within 1 hour of onset of symptoms or death before reaching medical care.

Risk factors, clinical descriptors, and drug therapy were considered individually to determine whether there were significant differences among the patients with and without QT >QS_2. For this analysis the standard 2 sample t test was employed for continuous data, whereas the distribution of dichotomous variables (chi-square test) was employed for discrete data. Each risk factor and clinical descriptor was also studied by univariate analysis for its capacity to discriminate differences in cumulative 5-year survival.[19,20] Those risk factors and clinical descriptors subjected to analysis were age, sex, arterial blood pressure, serum cholesterol, history of smoking, family history of coronary artery disease, history of diabetes, history of myocardial infarction before the reference myocardial infarction, New York Heart Association class for dyspnea, New York Heart Association class for angina pectoris, presence of S_4 gallop, presence of S_3 gallop, and electrocardiographic location of myocardial infarction. S_4 and S_3 gallops were considered present only when confirmed by phonocardiography. The administration of the following drug groups during the follow-up period was analyzed: diuretics, beta-blocking agents, nitrates, and antiarrhythmic agents. The following were considered the upper limit of normal in univariate survival analysis: serum cholesterol 250 mg/dl, and systolic arterial blood pressure 150 and diastolic 90 mm Hg. A smoking history was positive if the patient had smoked 1 or more packs of cigarettes per day for more than 1 year during 10 years before entering the study.

Variables found to be significantly different between the groups with and without QT >QS_2 by t test or chi-square analysis and those found to provide significant prognostic information by univariate life table analysis were subjected to multivariate analysis by the proportional hazards general linear model procedure developed by Mantel,[20] Peto,[21] and Harris et al.[22] The strategy of this multivariate analysis permits identification of predictors of survival after adjustment for the effects of other risk factors and thus affords an approach to the analysis of the contribution of associated risk variables to the prognostic potency of the QT >QS_2 in the same group of patients.

Results

Death occurred in 20 of the patients during the follow-up period. The cause of death was sudden in 16, congestive heart failure in 2, and recurrent myocardial infarction in 2. Among the nonsurvivors the incidence of QT >QS_2 (65%) was significantly greater than that among survivors (9%) ($p < 0.01$). Among the nonsurvivors the incidence of long QTc (20%) did not differ significantly from that among survivors (11%).

The 5-year cumulative survival curve for the entire patient group is shown in Figure 1. The overall survival for the group was 80%, corresponding to a cumulative mortality rate of 20%.

Twenty patients had QT >QS_2 and 80 patients had QT ≤QS_2. The cumulative 5-year survival curves for these groups are shown in Figure 2. The cumulative 5-year survival for patients with QT >QS_2 (35%) was significantly diminished compared with that for patients with QT ≤QS_2 (91%) ($p < 0.001$).

The cumulative survival curves for the 87 patients with normal QTc (Bazzett) and the 13 patients with prolonged QTc are shown in Figure 3. The cumulative survival in patients with increased QTc was slightly but not significantly lower than that of patients with normal

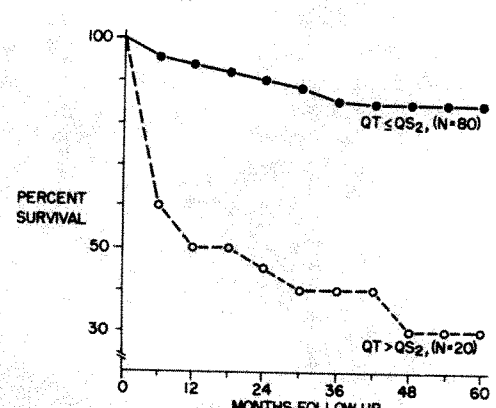


FIGURE 2. Cumulative 5-year survival rate for patients with and without QT >QS_2. The difference in survival curves is significant ($p < 0.001$).

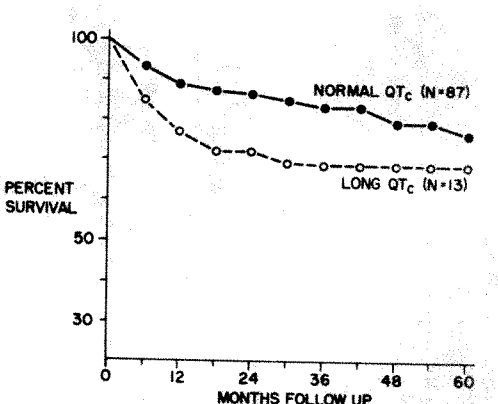


FIGURE 3. Cumulative 5-year survival rate for patients with normal and long electrical systole corrected for heart rate (QTc). The difference in survival curves is not significant.

QTc. Other equations for correcting the QT for heart rate were similarly less sensitive in stratifying the population into low and high risk groups (Table I).

Eleven patients had decreased total electromechanical systole corrected for heart rate (QS_2I), whereas 89 patients had normal QS_2I. The cumulative survival data for patients with normal or decreased QS_2I are shown in Figure 4. Survival in patients with decreased QS_2I

TABLE I Comparison of Cumulative 5-Year Survival by QT − QS_2 and QT Corrected for Heart Rate Using Various Equations

	Normal (%)	Abnormal (%)	p
QT − QS_2	91	35	<0.001
Bazzett[6] and Fenn[12]	82	69	NS
Fridericia[13]	82	69	NS
Ashman[7]	82	69	NS
Boudoulas et al[9]	82	69	NS

NS = not significant.

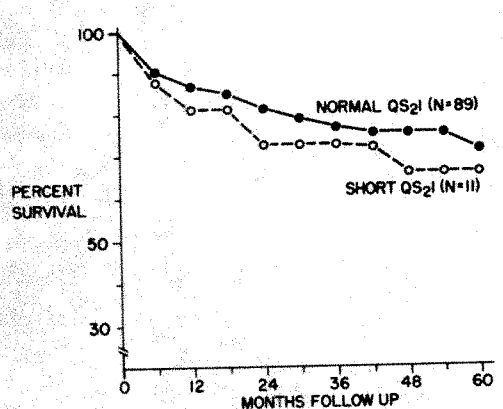


FIGURE 4. Cumulative 5-year survival rate for patients with normal and short electromechanical systole corrected for heart rate (QS_2I). The difference in survival curves is not significant.

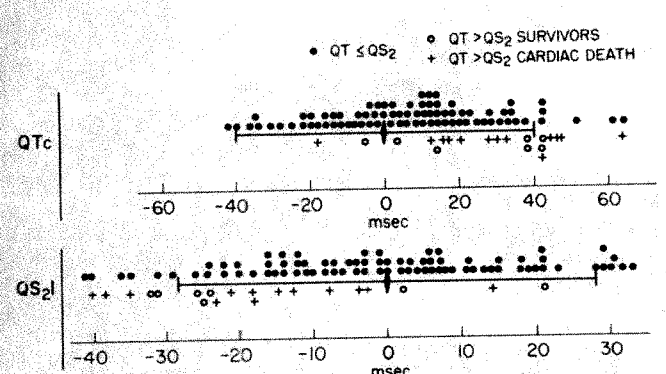


FIGURE 5. Distribution of electrical systole corrected for heart rate (QTc) and electromechanical systole corrected for heart rate (QS_2I) in 100 patients with and without QT >QS_2. Two standard deviations from the mean normal values (0 point) are shown. Patients with QT >QS_2 who died are indicated.

TABLE II Univariate Analysis Comparison of Patients With and Without QT >QS_2*

Variable	QT >QS_2 (n = 20) (%)	QT ≤QS_2 (n = 80) (%)	Probability
Sex			
Male	85	90	NS
Female	15	10	
Age (yr)			
≤60	70	80	NS
>60	30	20	
Mean	52.7 ± 8.3	53.1 ± 8.1	
Family history			
Absent	55	45	NS
Present	45	55	
History of previous MI			
Absent	80	82.5	NS
Present	20	17.5	
History of smoking			
Absent	30	22.5	NS
Present	70	77.5	
Diuretics			
Absent	45	50	NS
Present	55	50	
Beta-blocking agents			
Absent	65	50	NS
Present	35	50	
Nitrates			
Absent	5	1.3	NS
Present	95	98.7	
Antiarrhythmics			
Absent	80	85	NS
Present	20	15	
Vessels			
1	10	26.3	p <0.02
2	25	43.7	
3	65	30.0	
S_3			
Absent	75	88.7	NS
Present	25	11.3	
S_4			
Absent	60	50	NS
Present	40	50	
Systolic blood pressure			
Normal	75	86.2	NS
High	25	13.8	
Mean	128 ± 17	130 ± 18	NS
Diastolic blood pressure			
Normal	75	76.3	NS
High	25	23.7	
Mean	80 ± 9	81 ± 10	NS
Cholesterol			
Normal	55	39.2	NS
High	45	60.8	
Mean	264 ± 57	270 ± 60	
Angina			
Class I and II	60	61.2	NS
Class III and IV	40	38.8	
Angina			
Class I	30	23.8	NS
Class II, III, and IV	70	76.2	
Dyspnea			
Class I and II	75	81.2	NS
Class III and IV	25	18.8	
Dyspnea			
Class I	40	61.2	NS
Class II, III, and IV	60	38.8	
PEP/LVET			
Normal	20	53.7	<0.02
Abnormal	80	36.3	

* MI refers to myocardial infarction before reference myocardial infarction. Symptoms and clinical signs (angina, dyspnea, blood pressure, S_3, and S_4) refer to findings at time of the determination of QT and QS_2.

TABLE III Risk Factors and Clinical Descriptors Among Survivors and Nonsurvivors

Variables	Survivors (8 = 80)	Nonsurvivors (n = 20)
Sex		
Male	88.8%	90%
Female	11.3%	10%
	$\chi^2 = 0.02$	p = NS
Age (yr)		
≤40	6.3%	10.0%
>40	93.8%	90.0%
	$\chi^2 = 0.00$	p = NS
Age (yr)		
≤50	35.0%	45.0%
>50	65.0%	55.0%
	$\chi^2 = 0.32$	p = NS
Age (yr)		
≤60	81.3%	65.0%
>60	18.8%	35.0%
	$\chi^2 = 1.60$	p = NS
Family history		
Absent	51.3%	30.0%
Present	48.8%	70.0%
	$\chi^2 = 2.11$	p = NS
History of previous MI		
Absent	81.3%	70.0%
Present	18.8%	30.0%
	$\chi^2 = 0.63$	p = NS
Smoking		
Absent	23.8%	25.0%
Present	76.3%	75.0%
	$\chi^2 = 0.01$	p = NS
Diuretics		
Absent	55.0%	25.0%
Present	45.0%	75.0%
	$\chi^2 = 4.62$	p = 0.03
Beta blocking agents		
Absent	48.8%	80.0%
Present	51.3%	20.0%
	$\chi^2 = 5.11$	p = 0.02
Nitrates		
Absent	98.8%	95.0%
Present	1.3%	5.0%
	$\chi^2 = 0.03$	p = NS
Antiarrhythmic agents		
Absent	82.5%	90.0%
Present	17.5%	10.0%
	$\chi^2 = 0.22$	p = NS
Vessels		
1	40.0%	20.0%
2	35.0%	30.0%
3	25.0%	50.0%
	$\chi^2 = 5.22$	p = 0.07
S_3		
Absent	91.3%	65.0%
Present	8.8%	35.0%
	$\chi^2 = 0.06$	p = 0.007
S_4		
Absent	46.3%	40.0%
Present	53.8%	60.0%
	$\chi^2 = 0.00$	p = NS
Systolic blood pressure		
Normal	40.5%	50.0%
High	59.5%	50.0%
	$\chi^2 = 0.026$	NS
Diastolic blood pressure		
Normal	75.0%	80.0%
High	25.0%	20.0%
	$\chi^2 = 0.03$	p = NS
Cholesterol		
Normal	40.5%	50.0%
High	59.5%	50.0%
	$\chi^2 = 0.26$	p = NS
Angina		
Classes I and II	61.3%	60.0%
Classes III and IV	38.8%	40.0%
	$\chi^2 = 2.08$	p = NS
Angina		
Class I	21.3%	40.0%
Classes II, III, and IV	78.8%	60.0%
	$\chi^2 = 2.08$	p = NS
Dyspnea		
Classes I and II	83.8%	65.0%
Classes III and IV	16.3%	35.0%
	$\chi^2 = 2.44$	p = NS
Dyspnea		
Class I	65.0%	25.0%
Classes II, III, and IV	35.0%	75.0%
	$\chi^2 = 8.87$	p = 0.002
PEP/LVET		
Normal	56.3%	10.0%
Abnormal	43.8%	90.0%
	$\chi^2 = 11.94$	p = 0.0005
QT >QS_2		
Present	8.8%	65.0%
Absent	91.3	35.0%
	$\chi^2 = 28.22$	p = 0.0001
QTc		
Normal	83	17
Long	62	38
	$\chi^2 = 1.99$	NS
QS_2I		
Normal	80	20
Short	73	17
	$\chi^2 = 0.40$	NS

MI = myocardial infarction; NS = not significant; QS_2I = total electromechanical systole corrected for heart rate; QTc = electrical systole corrected for heart rate.

was slightly but not significantly lower than that of patients with normal QS_2I. Thus, although determination of QT >QS_2 stratified the patients into 2 distinct survival patterns, neither the QTc nor the QS_2I alone could significantly distinguish patients with high or low risk of mortality.

To define the relative contribution of QT lengthening and QS_2 shortening to the presence of QT lengthening relative to QS_2, patients with QT >QS_2 were analyzed relative to the distribution of QTc and QS_2I (Fig. 5). Among the 20 patients with QT >QS_2 the levels of QTc tended to cluster within the upper range of normal, whereas the QS_2I decreased within the lower range of normal. Abnormal lengthening of QTc occurred in 7 of the patients with QT >QS_2, whereas abnormal shortening of QS_2I occurred in 5. Therefore, the presence of QT >QS_2 proved to be a result of the combined influence of QT lengthening and QS_2 shortening without a dominant influence of either variable.

Univariate analysis for the significance of differences in risk factors and clinical descriptors among patients with and without QT >QS_2 is shown in Table II. The 2 variables that retained significant difference in the 2 groups were the PEP/LVET and the mean number of coronary arteries with >70% narrowing. Independent univariate survival analysis for each of these risk factors and clinical descriptors demonstrated that the same 2 variables in addition to QT >QS_2 had significant independent prognostic value. Comparison of the survivors with the nonsurvivors with respect to each of these risk factors and clinical descriptors demonstrated significant differences for the presence of QT >QS_2, ab-

normal PEP/LVET, dyspnea class, therapy with diuretics, and therapy with beta-blocking agents (Table III). Multivariate analysis by the proportional general linear hazards model revealed that of the foregoing variables, only PEP/LVET added significantly to the potential value of QT >QS_2 in stratifying the cumulative 5-year survival curves.

To further test the relative potency of the 2 variables, left ventricular resting performance by PEP/LVET and the occurrence of QT >QS_2 as survival predictors, the patients were divided into groups with normal and abnormal PEP/LVET and subdivided for the presence of QT >QS_2. Among the 47 patients with normal PEP/LVET only 4 had QT >QS_2, thus precluding accurate comparison of survival stratification by QT >QS_2 in this group. Among the 53 patients with abnormal PEP/LVET the group with QT >QS_2 (16 patients) was sufficiently large to allow a test of the independent influence of PEP/LVET and QT >QS_2 on survival. The data are summarized in Figure 6. Cumulative 5-year survival of patients with abnormal PEP/LVET and QT >QS_2 was significantly lower compared with that of patients with abnormal PEP/LVET in the absence of QT >QS_2 ($p < 0.01$). The average PEP/LVET and the mean number of coronary arteries with >70% narrowing did not differ significantly in these 2 groups (Table IV).

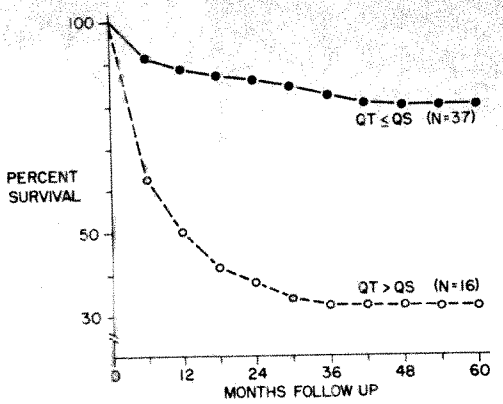


FIGURE 6. Cumulative 5-year survival rate for patients with abnormal left ventricular performance (preejection period/left ventricular ejection time, >0.42) with and without QT >QS_2. The difference in survival curves is significant ($p < 0.01$).

Discussion

In recent studies we demonstrated that measurement of systolic time intervals permits stratification of patients with previous myocardial infarction into widely divergent survival groups.[23] The cause of death among patients so stratified was dominantly sudden death. The prognostic potency of the systolic time interval measurement was greater than that of the extent of coronary arterial narrowing. These studies were consonant with those of Gillilan et al,[24] who similarly demonstrated a high level of stratification of patients with coronary artery disease into low and high risk groups by the measurement of systolic time intervals. On this basis, we focused attention on the potential value of additional noninvasive measures that might sensitize the prognostic potential of the systolic time intervals. Among these was the duration of electrical systole, the subject of the present investigation.

The current study documents that the presence of QT >QS_2 constitutes a significant risk factor in patients who have recovered from previous myocardial infarction. Further, it was documented that the use of the QS_2 as a normative reference lends a more sensitive prognostic index than that provided by equations that correct the QT interval for heart rate.

Analysis of the contribution of risk factors, clinical descriptors, and drug therapy in coronary artery disease to survival differences associated with normal and increased QT relative to QS_2 is pertinent to the question: does the presence of QT >QS_2 constitute an independent risk factor or is it a measure closely associated with other factors known to influence survival in coronary artery disease? Only 2 variables, the exent of coronary arterial occlusive disease and the presence of left ventricular dysfunction, proved significantly different among patients with and those without QT >QS_2. Each of these proved to be independent risk discriminators on 5-year cumulative survival analysis as well. When these 2 variables were compared with QT >QS_2 by proportional general linear analysis, only PEP/LVET added significantly to the QT >QS_2 in stratifying the cumulative 5-year survival curves.

An increase in the QT interval normalized for QS_2 yields a more direct expression of prolongation of the repolarization phase of electrical systole than can be derived from determinations of the QT interval corrected for heart rate. In calculating the difference between the durations of the QT and QS_2 intervals in the same beats, the duration of the QRS interval, a constant in both measures, is subtracted. In correcting the duration of the QT interval relative to heart rate, the QRS

TABLE IV Extent of Vessel Disease in Patients With and Without QT >QS_2 Subdivided for Presence of Left Ventricular Dysfunction

	PEP/LVET ≤0.42			PEP/LVET >0.42		
	QT >QS_2 (n = 4)	QT ≤QS_2 (n = 43)	p	QT >QS_2 (n = 16)	QT ≤QS_2 (n = 37)	p
Vessels*	1.75 ± 0.96	1.67 ± 0.75	NS	2.3 ± 1.1	2.10 ± 0.80	NS
Mean PEP/LVET	0.36 ± 0.03	0.37 ± 0.04	NS	0.53 ± 0.02	0.52 ± 0.02	NS

* Number of vessels with luminal narrowing of >70%. Values are expressed are mean ± standard deviation.

interval is included and contributes independently to the duration of the corrected or normalized QT interval. Thus, assessment for the presence of a prolonged repolarization phase by normalization for heart rate is limited by the inclusion of the duration of the depolarization interval in the calculation.

Prolongation of the QT interval as defined by its relation to the QS_2 interval might be accounted for by abbreviation in the QS_2 interval alone. Such a selective shortening of QS_2 relative to QT has in fact been observed during adrenergic stimulation of the heart, an effect that is blocked by propranolol.[10] However, the presence of QT >QS_2 among patients in this study was related to the coexistence of a relative lengthening of QT and a shortening of QS_2. Because increased adrenergic activity tends to selectively shorten the QS_2 interval with little influence on the QT,[10] it appears that enhanced adrenergic cardiostimulatory activity alone cannot explain the occurrence of QT >QS_2.

Among other mechanisms that may account for relative prolongation of electrical systole, localized or generalized delay in intramyocardial repolarization secondary to ischemic myocardial damage, autonomic factors, central nervous system influences, and antiarrhythmic drug therapy must also be considered. The role of the first 3 of these mechanisms was not elucidated in the present study. Regarding antiarrhythmic therapy, there was no significant difference in such therapy among patients with and those without QT >QS_2. On separate analysis there was no significant difference in antiarrhythmic therapy when survivors and nonsurvivors of the present study were compared.

In summary, our observations demonstrate that detection of prolongation of the QT interval, and more specifically of the repolarization phase of electrical systole employing the duration of electromechanical systole (QS_2) as a standard of reference, clinically defines a group of patients with prior myocardial infarction at hish risk of death. The QT interval corrected for the QS_2 is superior to the QT corrected for heart rate as a prognostic indicator. The improved prognostic potency of the QT interval corrected for QS_2 most probably reflects a more direct physiologic link between electrical repolarization and mechanical events of the cardiac cycle. The exact mechanism through which chronic ischemic heart disease contributes to prolongation of the QT interval relative to mechanical systole has yet to be defined. Although adrenergic influences may contribute, they cannot wholly explain the presence of QT >QS_2 among patients at high risk. Other factors probably play a significant role. The association of this finding with other indexes of electrical instability has yet to be defined.

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Transaxial Tomography With Thallium-201 for Detecting Remote Myocardial Infarction

Comparison With Planar Imaging

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Transaxial tomograhic imaging with thallium-201 was compared with standard, planar imaging in 38 patients with remote myocardial infarction and in 15 normal patients. Tomographic images were reconstructed from 64 views collected by a gamma camera that rotated about the anterior circumference of the patient's chest. A series of consecutive transverse-section images which encompassed the cardiac volume were reconstructed at a 6 mm plane spacing by filtered back-projection. No correction was made for attenuation losses. The set of transverse-section images was reformatted by 3-dimensional interpolation to obtain tomograms along the long and short axes of the myocardium. Tomographic and planar images were interpreted qualitatively.

Overall, tomography detected 33 of 38 (87%) prior infarctions whereas planar imaging detected 24 of 38 (63%) ($p = 0.01$). Improvement of the tomographic imaging method occurred only in the combined subset of transmural inferior and subendocardial infarctions, and not in transmural anterior infarctions. Peak increases in creatinine phosphokinase were smaller in patients detected only by tomography compared with those detected by both the planar and the tomographic approach (3.1 × normal versus 10.4 × normal, $p = 0.04$). Five patients (13%) with prior infarction were not detected by either approach. For 6 of the 9 patients detected by tomography alone, realignment of the image data along the short and long axes of the heart was essential for making the diagnosis. Fourteen of 15 patients without infarction were normal on both planar and tomographic imaging. A single normal patient had a defect detected by both techniques, yielding a specificity of 93% for each.

We conclude that transaxial tomography significantly improves the detection of thallium-201 myocardial perfusion defects in patients with prior myocardial infarction.

Thallium-201 is the current radionuclide of choice for the delineation of myocardial perfusion by gamma camera imaging. When injected after exercise or pharmacologic stress, regions of transient or reversible hypoperfusion may be identified in images taken immediately after isotope injection.[1-3] Imaging performed late after exercise-injection reflects a more basal distribution of blood flow; perfusion defects identified at this time usually define remote or prior myocardial infarction.[4,5] Similarly, defects identified by imaging performed at rest in stable patients demonstrate perfusion abnormalities that result from prior myocardial infarction.[6,7] The presence and extent of rest perfusion defects relate closely to quantitative indexes of prior myocardial infarction such as the extent and presence of regional contraction abnormalities.[6,7] In patients studied 6 to 12 months after acute myocardial infarction, the presence of a thallium-201 perfusion defect was more common than an identifiable wall motion abnormality or an electrocardiographic Q wave.[8] However, the planar imaging technique has inherent limitations. Considerable isotope is taken up by contiguous or nearby nonmyocardial structures such as lung and skeletal muscle. In planar imaging, this background or nonmyocardial activity to some extent overlaps myocardium in any given view and may mask the presence of perfusion abnormalities. Additionally, the truncated elliptical shape of the human heart dictates that some normal myocardium from an adjacent or opposing myocardial wall is partly superimposed on a given regional defect

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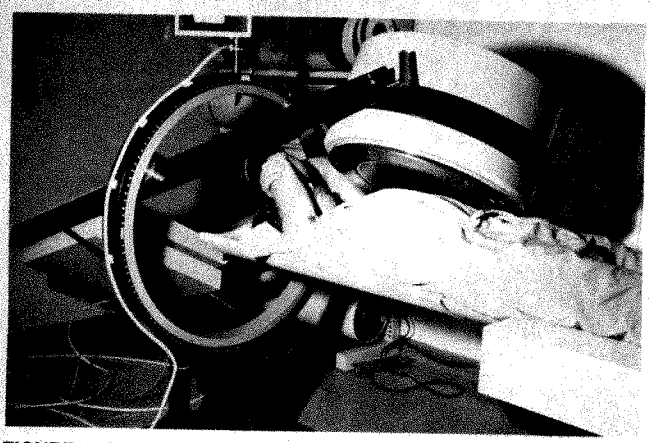

FIGURE 1. Gamma camera rotating about the patient for data collection. The camera is halfway through its rotation for collection of data about the anterior 180° of myocardium (see Figure 2).

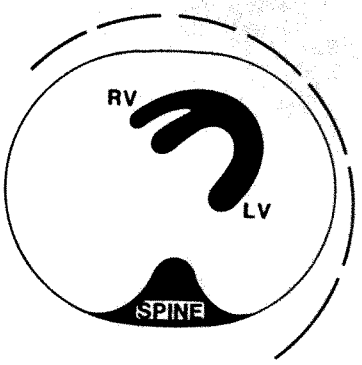

FIGURE 2. Schematic drawing of a transverse section through the thorax in the standard computed tomographic orientation. **Dashed line** indicates the 180° area over which image view data were collected. LV = left ventricle; RV = right ventricle.

and may similarly mask both the detection and the quantitation of perfusion deficits. Also, the low photon energy of thallium-201 results in considerable attenuation losses such that regions of the heart relatively deep in the body are underrepresented.

Transaxial tomography, an approach similar in theory to that of X-ray computed tomography, collects data circumferentially about 180 or 360° around the patient's chest; images are then reconstructed in discrete slices in the transaxial plane by computer techniques.[9–12] Reconstruction of these discrete transaxial slices should largely eliminate the problem of overlap of both adjacent normal myocardium and other noncardiac background structures. However, an accurate correction for attenuation losses in the thorax has yet to be accomplished for single photon studies (see later). In this study, we compared rest thallium-201 images obtained by the transaxial tomographic approach with standard planar images in the same patients with documented remote myocardial infarction. The purpose of this study was to ascertain whether qualitative analysis of transaxial tomographic images improves sensitivity or specificity in the detection of remote myocardial infarction compared with that of planar imaging.

Methods

Patient selection: Patients with prior myocardial infarction were selected from a clinic devoted to cardiovascular diseases by one of us as the first 38 patients agreeable to participate who fulfilled all of the following criteria: (1) either no or class I or II New York Heart Association stable angina pectoris; and (2) remote myocardial infarction identified by at least 2 of the 3 features: (a) electrocardiographic Q waves or S-T and T wave changes at the time of (b) an event characterized by prolonged and severe substernal chest pain and (c) elevation of creatinine phosphokinase to at least twice the normal value. These findings were ascertained by review of previous medical records by one of us.

These myocardial infarctions had occurred an average of 5.6 years before imaging (range 6 weeks to 12 years with all but 4 being 1 or more years). The peak creatinine phosphokinase level was known to be greater than twice normal in all but 2 of these patients. Because many of the events occurred in other hopsitals several years earlier, the magnitude of peak creatine kinase values were available in only 20 patients. Of the total of 38 patients with remote myocardial infarction, 16 had inferior, 11 had anterior, and 2 had combined anterior and inferior transmural myocardial infarction was evidenced by electrocardiographic Q waves of at least 0.03 second in duration in leads II, III, and aVF and/or the precordial leads, respectively. A single patient had isolated Q waves in leads I and aVL and was considered an anterior infarction. Three patients had inferior transmural myocardial infarctions with subsequent loss of diagnostic Q waves. These 3 patients were considered to have transmural infarction. Nine patients were designated as having had nontransmural infarction on the basis of S-T and T wave changes only without the development of new Q waves. In 4 of these cases ST-T wave changes were generalized; in 2 they were localized to the precordial leads and in 3 to the inferior leads. Fifteen patients without evidence of prior myocardial infarction were also studied. Eight of these patients were normal young volunteers under age 40 years who had no symptoms or signs of cardiovascular disease and who had normal electrocardiograms. Seven were patients who had undergone coronary angiography for suspected coronary disease but who had normal coronary arteries and normal left ventricular contraction patterns. All patients were advised of the experimental nature of the protocol and gave informed consent approved by the University of Washington Human Subjects Review Committee.

Image collection: One and a half microcuries of 201-thallous chloride was injected intravenously with the patient standing and after an overnight fast. Within 5 to 10 minutes, the patient was positioned on the imaging table and data collection started with a wide field of view camera (General Electric 400T, Milwaukee, Wisconsin) mounted on a rotating gantry positioned so that it could rotate freely about 360° around the patient's thorax. The camera head was adjusted to most closely approximate the left chest wall at the cardiac apex and yet clear the extreme right and left sides of the chest when rotated circumferentially about the body (Fig. 1 and 2). This positioning involved a fixed radius of rotation of 22 cm in diameter; the height of the table was adjusted for each patient to bring the camera head as close as possible to the chest wall at the apex of the heart.

The radius of rotation was monitored by a potentiometer mounted on one of the arms attaching the detector to the gantry. The voltage across the potentiometer was measured

by a 4-digit digital voltmeter. Variation of arm angle during data collection was better than 1 part in 300. Following the observation of Larsson,[13] who noted that virtually no cardiac thallium-201 activity was collected over the 180° farthest from the myocardium, we collected data only over the anterior myocardial 180° (Fig. 2). The long axis of the heart was assumed to approximate a 30° angle from the frontal plane, and image data were collected over 90° to either side of this angle (Fig. 2). A total of 64 discrete view images, that is, 1 image every 2.8°, were acquired over 180°. The image format was 128 by 128 and the counting rate was approximately 2,000 counts/s. With the high resolution, low energy collimator (round hole version), each image was acquired for 20 seconds for a total acquisition time of under 22 minutes. Immediately after tomographic collection, standard planar images were acquired on an Ohio Nuclear Series 100 scintillation camera equipped with an all purpose, low energy collimator. Anterior, 30° left anterior oblique, 45° left anterior oblique, and 60° left anterior oblique views of 300,000 counts each were obtained and displayed on tri-lens Polaroid film. In 9 patients, only 3 planar views were obtained because of prolonged set-up time early in the study. In each of these 9 cases, a defect was either present in multiple views or not present in any view, and the collection of an additional view would not have modified our interpretation (see later). Previous study in our laboratory has shown that in patients with stable, remote myocardial infarction injected at rest, images remain unchanged over a period of 1.5 to 2 hours[14]; that is, the presence of the defect is stable over the period of imaging. In 8 of the normal patients, the only images employed were those obtained at redistribution 2 to 3 hours after initial injection during treadmill exercise. Previous study in our laboratory showed that redistribution and rest images in normal patients were both normal and essentially identical.[5] The remaining 7 normal patients in this series had redistribution as well as separate rest images, which were visually identical.

Image processing: The projection images were low-pass filtered to reduce statistical noise by a 5 by 5 spatial convolving kernel with a frequency cutoff of 0.285 cycles per projection pixel. For each transverse section reconstructed, the corresponding 128-point projection arrays from each view were Fourier-domain filtered in a firmware array processor by a linear ramp that cut off sharply at the Nyquist frequency in reconstruction space (0.285 cycles per projection pixel). Each filtered projection was adjusted for center-of-rotation[15] and back-projected into a 64 by 64 image matrix. No noise smoothing was incorporated into the projection filtering. The set of transverse-sections reconstructed bracketed the cardiac volume in increments of 6 mm (every other axial projection pixel). These images were further processed to obtain tomograms in 3 orthogonal perspectives aligned with respect to the cardiac axes by the method developed in our laboratory by Olsen et al.[16] Thus, superior long axis, right anterior oblique long axis, and short axis cardiac tomograms were available for interpretation. This realignment provides no additional data, but simply displays them in an anatomically oriented format in which abnormalities of perfusion are more easily assimilated.

We did not employ computer processing in the analysis of the planar images, as an earlier study from our laboratory had shown no significant improvement over analysis of the tri-lens Polaroid format.[14]

Image interpretation: All images were interpreted qualitatively by 2 observers unaware of clinical information. A perfusion defect was defined as a discrete regional count deficit visually estimated at ≥50% that of adjacent walls and encompassing ≥20% of the circumference of the myocardium, present in at least 2 views on the planar studies and at least 2 slices on the tomographic studies, as previously defined in our laboratory in several series.[2,5,7,14] In 4 cases there was observer disagreement and a consensus was employed.

TABLE I Thallium-201 Transaxial Tomography: Type and Location of Myocardial Infarction (n = 38)

	Tomography Only (n = 9)	Planar and Tomographic Imaging (n = 24)	Not Detected (n = 5)
AMI	1	12	...
DMI	4	11	1
SEMI	4	1	4

AMI = anterior myocardial infarction; DMI = diaphragmatic or inferior myocardial infarction; SEMI = subendocardial myocardial infarction.

Results

Among the 38 patients with prior myocardial infarction, 24 (63%) had perfusion abnormalities on both transaxial tomographic and planar imaging. In 9 patients (24%), perfusion defects were identified by tomography but not by planar imaging. In 5 patients (13%), tomographic as well as planar images were entirely normal (Table I, Fig. 3). In no patient was a defect seen on planar images and not on tomographic study. Overall sensitivity in the detection of prior myocardial infarction by the tomographic technique was 33 of 38 (87%) and by the planar technique 24 of 38 (63%). The detection of defects by the tomographic approach was statistically significantly greater at the $p = 0.01$ level (McNemar test of correlated proportions). In the 15 patients without myocardial infarction, all but 1 patient was correctly identified as normal by each technique. That patient had an inferior defect on both tomography and the planar approach and had typical exertional angina and normal coronary arteries. Specificity was thus 93% for both the tomographic and the planar approaches.

The type of infarction (transmural or subendocardial) and location are shown in Table I. Four of the 5 patients with prior infarction not detected by either imaging modality had subendocardial infarction; the fifth had

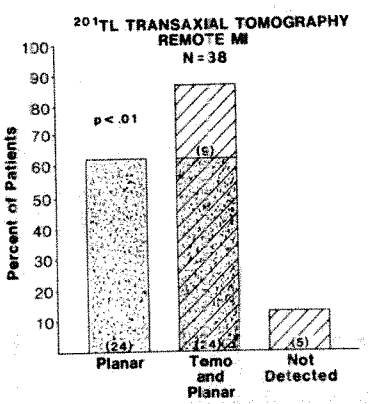

FIGURE 3. Of patients with prior infarction 63% were detected by planar imaging (**left**), 87% by tomography (Tomo) (**center**), and 13% were not detected by either approach (**right**). MI = myocardial infarction.

an inferior transmural infarction. Four of the 9 patients (44%) whose infarction was detectable only by tomography had subendocardial infarctions. The remaining 5 patients detected only by tomography had transmural infarction and 4 of these 5 were inferior. Of the 24 patients with infarctions detectable by both planar and tomographic imaging, only 1 (4%) had a subendocardial infarction. When patients with inferior and subendocardial infarctions were considered together, significantly more infarctions were detected by the tomographic (20 of 25, 80%) than the planar approach in this subset (12 of 25, 48%; $p = 0.01$, McNemar test). This was not the case for anterior transmural infarctions as only 1 of 13 such patients had detection by tomography alone. The distribution of patients with subendocardial myocardial infarctions localized electrocardiographically did not differ in the 3 groups, although the number of cases was small.

In those patients identified only by tomography, peak creatinine kinase was 3.1 ± 1.5 (standard deviation) times normal ($n = 6$) versus 10.4 ± 7.8 times normal ($n = 11$) in patients identified by both tomography and planar imaging ($p = 0.04$, Student's t test). The mean time between infarction and imaging, however, did not differ in these 2 groups (5.2 ± 2.8 years tomography alone versus 4.5 ± 4.0 years tomography and planar detection, p = not significant). All 3 patients in whom electrocardiographic Q waves disappeared over time were in the group detected by both planar and tomographic approaches. This number was too small for statistical analysis.

Additionally, in the 9 patients with perfusion defects seen only on tomography, 6 (67%) were identified only in the images realigned along the principal long and short cardiac axes. The sensitivity for detection of infarction by transverse or transaxial tomograms was 27 of 38 (71%) compared with 33 of 38 (87%) for the realigned tomograms. This figure represented a statistically significant difference at the $p = 0.05$ level. Thus, most of the improvement in sensitivity with the tomographic approach required realignment along the principal myocardial axes.

Figure 4 illustrates a patient with a prior transmural diaphragmatic myocardial infarction in whom the planar images were normal. The tomographic study, however, showed a definite inferior perfusion defect, seen best on the short axis and right anterior oblique long axis perspectives and not clearly defined in the reconstructed transaxial images. Figure 5 illustrates a patient with an inferior, transmural myocardial infarction. Although the planar images were interpreted as showing a perfusion defect, it was poorly defined (Fig. 5A). The defect is not seen in the transaxial tomographic slices (Fig. 5B). The short axis tomographic image, however, clearly identifies an inferior abnormality present in 3 discrete slices (Fig. 5C).

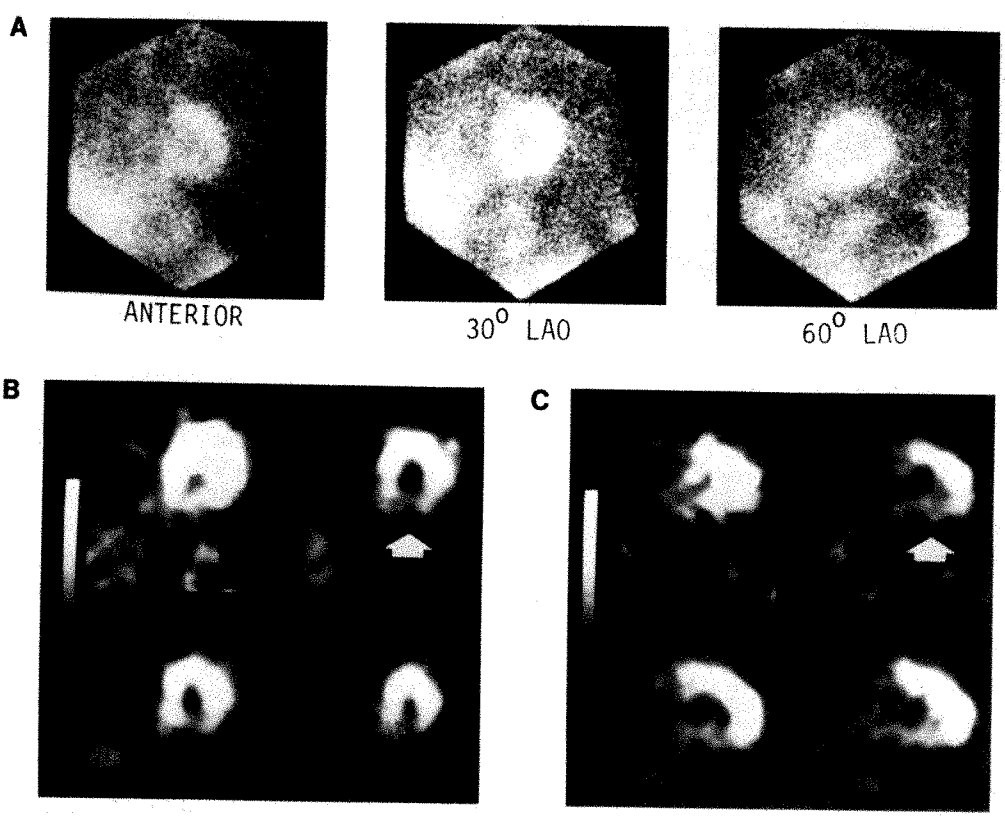

FIGURE 4. Patient with prior transmural inferior myocardial infarction. **A**, the planar images are normal. **B**, short-axis tomographic slices begin at the base (**upper left**) and work toward the apex (**upper right, lower left, lower right**); a defect is seen in 1 slice shown by the **arrow**. **C**, right anterior oblique slices (perpendicular to the short axis beginning with the right ventricle and septum and slicing toward the lateral wall). The inferior defect is shown by the **arrow**.

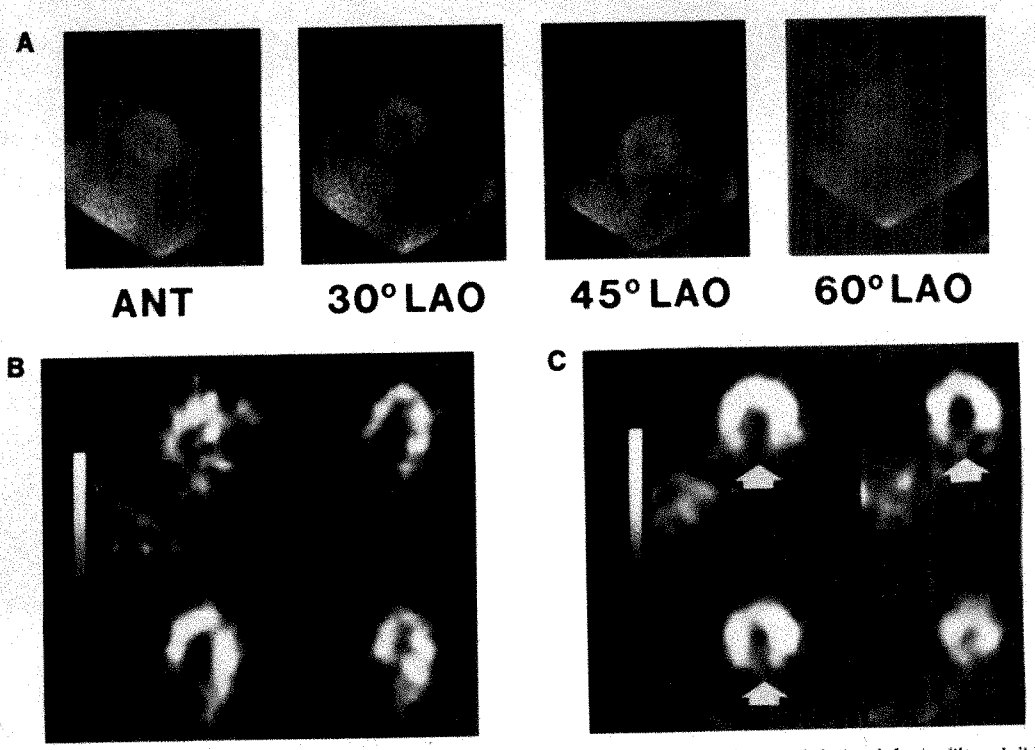

FIGURE 5. Patient with a transmural inferior myocardial infarction. **A**, planar images were read to show an inferior defect, although it is poorly visualized. (Reproduced with permission from Olson et al.[16]) **B**, transaxial slices beginning toward the feet (**upper left**) and working upward (**upper right, lower left, lower right**) do not clearly show an abnormality. **C**, short-axis views show a clear, well-demonstrated inferior defect in 3 slices (**arrows**).

In all cases, the anatomic location of perfusion defects was concordant when present in both planar and tomographic studies and corresponded with the electrocardiographic location of Q waves. In 3 of the tomographic studies, however, defect size appeared visually more extensive than that seen on the planar study.

Discussion

In this study of a gamma camera-based transaxial tomographic system, we assessed stable patients with remote myocardial infarction. In an earlier evaluation of the 7-pinhole approach to emission tomography, we showed that repeat tomograms obtained over a 1.5 to 2 hour period were stable and identical.[14] Thus, in the current study we compared a single transaxial tomographic study with standard planar scintigraphy performed at rest. The 7-pinhole or limited-angle approach to tomography did not yield improved sensitivity or specificity in the detection of remote myocardial infarction when studied in 48 patients (a series similar in size to the prsesent study) in our laboratory.[14] In contrast, transaxial tomography appears to offer improved sensitivity in the detection of perfusion defects in this preliminary series. The collection of data for 180° about the object fulfills the mathematic requirements for tomography as initially proposed by Radon[17] in 1917; that is, the object is viewed or imaged from all sides or perspectives, as distinguished from the 7-pinhole approach in which data are sampled over a maximal angle of about 85°. Of particular importance in the present approach was the realignment of the reconstructed transaxial images along the 3 orthogonal long and short axes of the heart. Perfusion defects often involve the inferoapical cardiac surface, which may fall entirely within a single transaxial slice and thus be hard to define; that is, a slice through the defect may show no myocardial activity, whereas the adjacent slice may then appear relatively uniform, without a definite perfusion defect, as shown in the transaxial slices in Figure 5B. Reorientation of the slice axes to coincide with the myocardial long and short axes best allows direct comparison of 1 wall to the opposite wall, and in the 2 long axis views, allows ready appreciation of apical abnormalities. Commonly, the short axis display most clearly separates perfusion defects into the coronary arteriographic beds as shown by the example in Figure 5C in which a defect involving the distribution of the posterior descending coronary artery (the inferior portion of the septum) is clearly shown.

As anticipated, myocardial infarctions detected by tomography alone appeared to be smaller than those detectable by both the tomographic and the planar approaches as evidenced by lower peak creatinine kinase values and the predominance of inferior and subendocardial infarctions. Studies by Niess et al[6] as well as our own earlier report[7] have shown a sensitivity of greater than 90% in the detection of infarction associated with electrocardiographic Q waves. The identification of 63% of all infarctions in this series is similar to the 75% sensitivity of Niess et al[6] for combined transmural and nontransmural infarctions and is similar to our earlier report identifying 69% of remote infarctions in a series of transmural and nontransmural in-

farctions.[14] Tiefenbrunn et al[8] reported a higher sensitivity; it seems likely that patient selection factors explain these differences and that our ambulatory population included more patients with smaller infarctions than some other series. Mueller et al,[18] in a related experimental model of canine myocardial infarction, found that ischemic zones of less than 5 g were not identified by planar imaging.

Single-photon transaxial tomography has been performed in both experimental and clinical settings for over a decade, initially by Kuhl and Sanders,[9] who demonstrated improved detectability of cerebral mass lesions. Similarly, Keyes,[10] Burdine,[11] Budinger,[12] Holman,[19] and their co-workers have reported feasibility and early clinical experiences. These early investigators used either uniquely designed systems or non–gamma camera-based systems. The current study employed a commercially available, gantry-suspended rotating gamma camera. This system and others like it are now becoming generally available at a cost only moderately higher than that of the gamma camera alone. Because the gamma camera may also be used for standard imaging, wide clinical use is feasible. The reconstruction software used for our study was implemented locally on a standard nuclear medicine computer system (Medical Data Systems A^2 computer, Ann Arbor, Michigan). Other reconstruction algorithms for this gamma camera system are available; that developed by Larsson[13] was recently described in detail.

We employed no attenuation correction in these studies but followed the observation of Larsson[13] and collected view data only over the 180° angular interval most anterior to the myocardium. Image quality was satisfactory, probably reflecting the relative centering of the heart with respect to soft tissue and body attenuation in the thoracic wall (Fig. 2). Without an attenuation correction, absolute quantitation of regional myocardial perfusion is not possible. To date, no satisfactory approach to this problem for the thorax has been implemented. Attenuation losses in the 180° of view data most distant from the heart are considerable. These data add little other than noise to reconstruction, and when combined with the anterior view data, reconstruction quality is degraded (unpublished observation).

In conclusion, this preliminary clinical study of patients with prior myocardial infarction supports the thesis that single-photon transaxial tomography improves the detection of perfusion defects with thallium-201. The collection of data for only the anterior 180° about the heart as well as reorientation of the tomographic images along the long and short axes of the myocardium were important contributing features to this improvement. It is not known whether the relatively long data collection time of 22 minutes will allow the application of this approach to transient perfusion abnormalities induced by exercise, but this subject deserves study.

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Noninvasive Detection of Multivessel Disease After Myocardial Infarction by Exercise Radionuclide Ventriculography

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The ability of exercise radionuclide ventriculography to detect multivessel coronary artery disease in patients who survived a single myocardial infarction was assessed. Seventy-four patients who had had myocardial infarction at least 8 weeks earlier underwent cardiac catheterization and exercise radionuclide ventriculography. Thirty-eight patients had had an inferior infarction: 25 with multivessel disease and 13 with single vessel disease of the right coronary artery. Thirty-six patients had had an anterior infarction: 26 with multivessel disease and 10 with single vessel disease of the left anterior descending coronary artery.

Among patients with anterior infarction there was no significant difference between patients with single vessel disease and patients with multivessel disease with regard to resting ejection fraction, exercise ejection fraction, and the mean change from rest to exercise. Patients with single vessel disease had a decrease in ejection fraction from rest to exercise of 2.2 ± 2.7% units (mean ± standard error [SE]), compared with a decrease of 5.4 ± 1.3% units in those with multivessel disease (p = not significant [NS]). Seventeen of 26 (65%) patients with multivessel disease and 6 of 10 (60%) with single vessel disease had a decrease in ejection fraction of at least 5 percentage units (p = NS).

In patients with inferior infarction there was no difference in the mean resting ejection fraction in those with single vessel disease (53 ± 2%) compared with those with multivessel disease (50 ± 2%); however, the mean exercise ejection fraction in patients with single vessel disease (57 ± 3%) was significantly higher (p <0.005) than that in patients with multivessel disease (45 ± 2%). Sixteen of the 25 patients with multivessel disease (64%) but only 1 patient with single vessel disease (7.7%) had a decrease in ejection fraction of at least 5 percentage units (p <0.001).

A new wall motion abnormality developed in 8 patients with anterior infarction and 11 with inferior infarction with multivessel disease and none with single vessel disease. The sensitivity and specificity in predicting multivessel disease using the criteria of the development of a new wall motion abnormality or a decrease in ejection fraction with exercise of at least 5 percentage units were 80 and 92% for the patients with inferior infarction, but only 69 and 40% for the patients with anterior infarction.

These results suggest that exercise radionuclide angiography can be used to discriminate between single and multivessel disease after inferior myocardial infarction. For patients with anterior infarction, only a new abnormality in wall motion accurately predicts multivessel disease, but this occurred in only one third of such patients.

The long-term prognosis of patients who survive myocardial infarction depends on the extent of coronary artery narrowing and the degree of left ventricular dysfunction.[1-3] The application of coronary artery bypass to improve prognosis in selected patients with multivessel disease has stimulated interest in identifying them from within the overall group of survivors of infarction.

Exercise radionuclide ventriculography has been shown to be a reliable noninvasive tool for diagnosing significant coronary artery disease.[4,5] However, its role in predicting the extent of disease in patients who have had a myocardial infarction remains unclear. In this study we evaluated the ability of exercise radionuclide ventriculography to detect multivessel disease after myocardial infarction.

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Methods

Study population: The study group consisted of 74 consecutive patients, 70 men and 4 women, with a mean age of 52 years (range 30 to 71) referred for coronary arteriography for various reasons including chest pain, evaluation of the extent of coronary artery disease, age, and arrhythmias. All patients had had a single myocardial infarction at least 2 months before the study. Myocardial infarction was documented by history, hospital records, and residual, significant (≥0.04 mm) Q waves on the resting electrocardiogram. Thirty-eight patients had had inferior infarctions and 36 anterior infarctions. Testing was performed within 6 months after infarction in 29, at 6 months to 1 year in 15, and after 1 year in 30. The mean time after infarction was 17 months in patients with inferior and 22 months in those with anterior myocardial infarction. Exercise radionuclide ventriculography was performed within 1 week of coronary arteriography in all patients.

Coronary arteriography: Selected coronary arteriography was performed using the percutaneous femoral technique in all patients. Studies were independently reviewed by 2 experienced angiographers without knowledge of the radionuclide results. Coronary stenosis was considered significant when luminal diameter was narrowed ≥70% (except in the left main coronary artery, where 50% narrowing was considered significant). Patients with disease of the left main coronary artery were classified as having multivessel disease.

Rest and exercise imaging procedure: In vivo labelling of red blood cells with 25 to 30 mCi of technetium-99m pertechnetate was accomplished by injecting this radiopharmaceutical 20 minutes after intravenous administration of 7.5 mg of stannous pyrophosphate. Gated radionuclide ventriculograms were obtained using a portable scintillation camera (Ohio Nuclear Series 420) with an all-purpose parallel hole collimator interfaced to a Medical Data Systems computer (A^2). The camera was positioned to obtain the left anterior oblique view that maximized separation of ventricular images. Gated images were acquired over 2 minute intervals, at 20 frames per cardiac cycle, at rest, and during the last 2 minutes of each 3 minute stage of graded supine bicycle exercise. Only the study acquired at peak exercise was used for analysis.

The left ventricular time activity curve was generated using a conventional software program (Medical Data Systems) containing semiautomatic edge detection and computer-determined background algorithms. Left ventricular ejection fraction was automatically calculated directly from the time activity curve. This method correlates well with results obtained in our Cardiac Catheterization Laboratory when compared with single plane contrast ventriculography in 50 consecutive patients ($r = 0.89$) (unpublished results).

Wall motion was evaluated by viewing the cardiac cycle in a loop movie format by 2 independent experienced observers without knowledge of cardiac catheterization data. The rest and peak exercise studies were viewed side by side to detect the development of an exercise-induced wall motion abnormality in 1 of 3 anatomic sites: septal, inferoapical, and posterolateral (Fig. 1). Because all of our patients had septal and inferoapical resting wall motion abnormalities after anterior myocardial infarction, a new abnormality was considered only when it occurred in the posterolateral wall; likewise, a new abnormality was considered only when it occurred in the septal region in patients after inferior myocardial infarction. Wall motion for each region was graded as follows: 3 = normal, 2 = mild hypokinesia, 1 = moderate to severe hypokinesia, 0 = akinesia, and −1 = dyskinesia. A change in score of at least 2 grades was considered to represent an exercise-induced abnormality. Agreement was exact in 81% (180 of 222) of regions. Differences in the remainder of the regions were resolved by joint review and arbitration of the studies by a third observer.

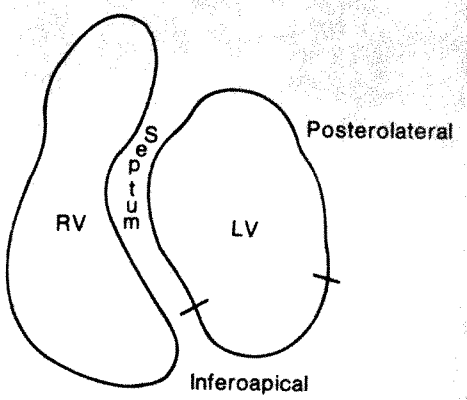

FIGURE 1. Schematic division of the left ventricle (LV) into septal, inferoapical, and posterolateral regions. RV = right ventricle.

Exercise protocol: Maximal graded supine bicycle exercise was performed starting at a work load of 200 kg-m/min and was increased by 200 kg-m/min increments every 3 minutes. Exercise was continued until the development of angina pectoris, dyspnea, or fatigue. Electrocardiographic recordings were obtained continually (lead II) during exercise and for 5 minutes after exercise. Administration of long-acting nitrates was stopped at least 8 hours before this study, but that of beta-blocking drugs was continued.

Analysis of data: All statistical analyses were performed with the Statistical Analysis System. For qualitative variables (such as sex) which are expressed as percentages, the chi-square test of association in contingency tables was used to test for differences between the groups. The quantitative data are presented as means ± standard error of the means. For quantitative variables, a least-squares analysis of variance was employed to compare the means. Covariance analysis was used to adjust means for differences between the groups on the basis of following variables: age, time since myocardial infarction, and use of beta-blocking drugs. For the principal outcomes of this study, a probability level of $p < 0.05$ was considered significant.

Results

Coronary angiography: Among patients with anterior myocardial infarction, 26 had multivessel disease which was distributed as follows: left main artery stenosis, 5 patients; triple vessel disease, 16 patients; double vessel disease with left anterior descending and right coronary artery involvement, 5 patients. The remaining 10 patients had single vessel left anterior descending artery disease. All patients had segmental wall abnormalities on contrast ventriculography consistent with prior anterior or anteroseptal myocardial infarction.

Among patients with inferior myocardial infarction, 25 had multivessel disease: left main stenosis in 9 patients, triple vessel disease in 12, and double vessel disease with left anterior descending and right coronary involvement in 4. Thirteen patients had disease isolated to the right coronary artery. All patients had inferior

TABLE I Clinical and Exercise Data

	Anterior MI		Inferior MI	
	SVD	MVD	SVD	MVD
Number	10	26	13	25
Male patients (%)	100	92.3	84.6	100
Beta-blocking drugs (% of patients)	50.0	53.9	61.5	68.0
Angina (exercise-induced) (%)	30.0	42.3	30.8	44.0
Peak HR (beats/min)	109.9 ± 6.4	109.0 ± 3.0	106.6 ± 5.7	103.0 ± 8.6
DP	159.8 ± 11.8	174.8 ± 7.7	172.2 ± 14.1	163.8 ± 8.1
	$p < 0.03$		$p < 0.10$	
Exercise duration (min)	8.9 ± 1.3	6.0 ± 0.5	8.7 ± 0.9	6.8 ± 0.5

Values are expressed as mean ± standard error of the mean. DP = double product; HR = heart rate; MI = myocardial infarction; MVD = multivessel disease; SVD = single vessel disease.

wall motion abnormalities on contrast ventriculography.

Exercise radionuclide ventriculography: anterior myocardial infarction: Among the patients who had anterior myocardial infarction there was no significant difference between those with multivessel and those with single vessel disease with regard to the percentage receiving beta-blocking agents, the peak exercise heart rate or double product, or the percentage of patients in whom exercise-induced angina developed (Table I). On the average, those with single vessel disease were able to exercise longer (8.9 ± 1.3 minutes versus 6.0 ± 0.5 minutes) ($p < 0.03$), but there was considerable overlap between groups.

The mean resting ejection fraction was similar in the 2 groups (multivessel 40 ± 2%, single vessel 45 ± 3%). All patients demonstrated wall motion abnormalities in both the septal and inferoapical regions. The mean peak exercise ejection fraction in the patients with multivessel disease was somewhat lower (34 ± 2%) than that in those with single vessel disease (43 ± 3%) (Fig. 2), but this difference did not achieve statistical significance ($p < 0.10$). The magnitude and direction of the ejection fraction response to exercise, however, did not

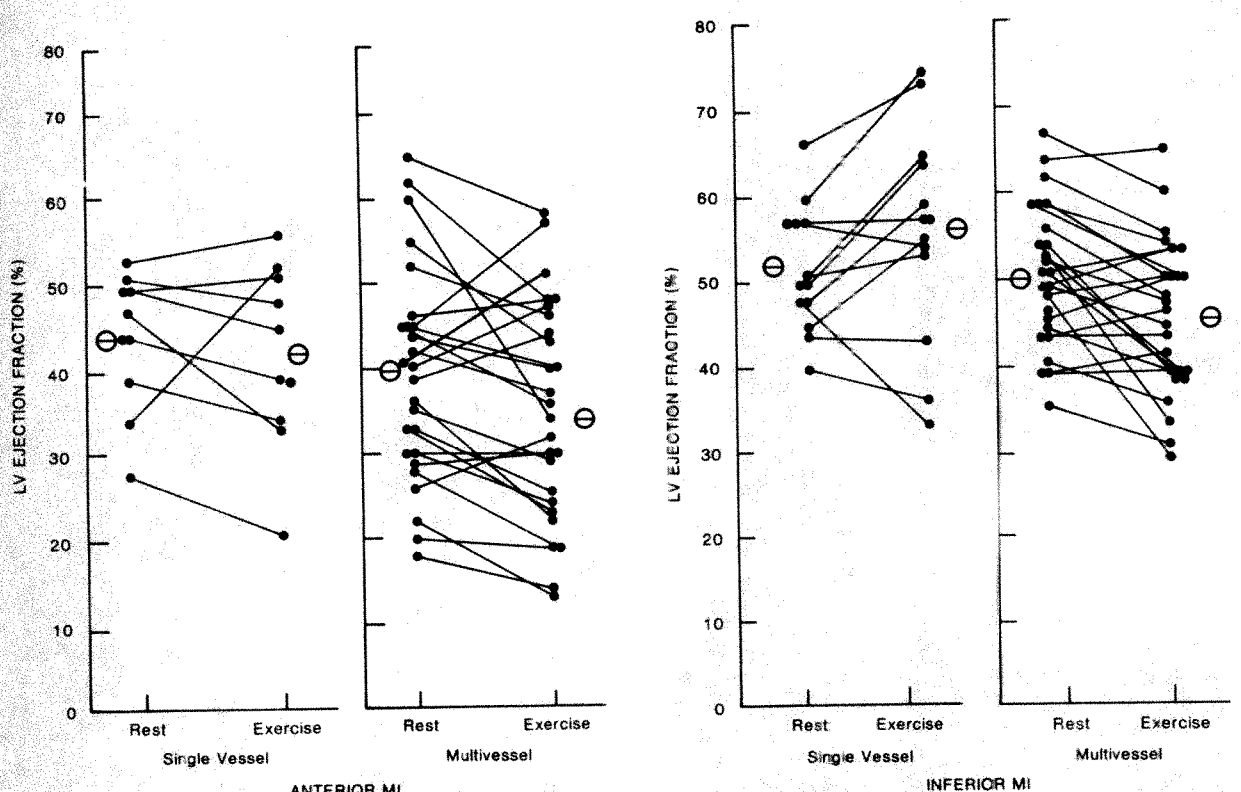

FIGURE 2. Resting and exercise ejection fractions in patients (**left**) after anterior myocardial infarction (MI) and (**right**) after inferior myocardial infarction. Only patients after inferior myocardial infarction with single vessel disease had an increase in ejection fraction with exercise. LV = left ventricular.

TABLE II Ejection Fraction (EF) and Wall Motion Results

	Anterior MI		Inferior MI	
	SVD	MVD	SVD	MVD
Number	10	26	13	25
Rest EF (%)	45 ± 3	40 ± 2	53 ± 2	50 ± 2
		p <0.1		p <0.004
Exercise EF (%)	43 ± 3	34 ± 2	57 ± 3	45 ± 2
				p <0.01
Δ EF	−2.2 ± 2.7	−5.4 ± 1.3	+3.8 ± 2.5	−5.2 ± 1.4
				p <0.001
% ↓5 units	60.0	65.4	7.7	64.0
		p <0.05		p <0.005
% developing new WMA	0.0	30.8	0.0	44.0

Values expressed as mean ± standard error of the mean. ΔEF = mean ejection fraction change from rest to exercise; MI = myocardial infarction; MVD = multivessel disease; % ↓5 units = percentage of patients with a decrease in ejection fraction of at least 5 percentage units; SVD = single vessel disease; WMA = wall motion abnormality.

distinguish the patients with single vessel disease from those with multivessel disease. The mean change in ejection fraction in response to exercise was −5.4 ± 1.3 units in patients with multivessel disease and −2.2 ± 2.7 units in those with single vessel disease (p = NS). Of particular interest is that even a marked exercise-induced decrease in ejection fraction of ≥5 units did not separate multivessel disease patients from those with single vessel disease. Seventeen of 26 (65%) patients with multivessel disease and 6 of 10 (60%) with single vessel disease had a decrease in ejection fraction from rest to exercise of ≥5 percentage units. Thus, in this important variable there was no difference between patients with single and multivessel disease (Table II).

A new wall motion abnormality developed in 8 of 26 (30.8%) patients with multivessel disease, but none in patients with single vessel disease (Table II). Combined analysis of the exercise ejection fraction response and wall motion changes in patients with multivessel disease revealed a new wall motion abnormality alone in 1 patient, an ejection fraction decrease of ≥5 units without a wall motion change in 10 patients, and both a new wall motion abnormality and a marked ejection fraction decrease in 7 patients. Thus, using both ejection fraction and wall motion analysis criteria, radionuclide testing correctly predicted multivessel disease in 18 of 26 patients (69%) while incorrectly predicting single vessel disease in 6 of 10 patients (sensitivity 69%, specificity 40%).

Inferior myocardial infarction: There were no significant differences between patients with multivessel and those with single vessel disease with regard to the percentage taking beta-blocking drugs, peak exercise heart rate, double product, or the percentage in whom exercise-induced chest pain developed. Patients with single vessel disease were able to exercise slightly longer than those with multivessel disease (8.7 ± 0.9 versus 6.8 ± 0.5 minute) (p <0.10) (Table I).

The mean resting ejection fractions were similar in both groups (multivessel 50 ± 2%, single vessel 53 ± 2%). All patients demonstrated inferoapical wall motion dysfunction. In contrast to those patients with anterior myocardial infarction, the ejection fraction response to exercise in patients with single vessel disease differed significantly from that in patients with multivessel disease (Fig. 2). The mean exercise ejection fraction increased from 53 ± 2% to 57 ± 3% in patients with single vessel disease whereas it decreased from 50 ± 2% to 45 ± 2% in patients with multivessel disease. The mean change in ejection fraction was significantly different in the 2 groups, patients with single vessel disease having an absolute increase of 3.8 ± 2.5 units compared with a decrease of 5.2 ± 1.4 in patients with multivessel disease (p <0.01). Sixteen of the 25 patients with multivessel disease (64%) but only 1 patient with single vessel disease (7.7%) had a decrease in ejection fraction with exercise of ≥5 percentage units (p <0.01) (Table II). Therefore, the sensitivity and specificity for predicting multivessel disease were 64% and 92.3% for a decrease in ejection fraction of ≥5%.

Table II demonstrates further that during exercise in 11 patients (44%) with multivessel disease a new septal wall motion abnormality developed indicative of disease in the left anterior descending artery. No new wall motion abnormalities were seen in those with only single vessel disease. Combined analysis of the exercise ejection fraction response and wall motion changes in patients with multivessel disease revealed a new wall motion abnormality alone in 4 patients, an ejection fraction decrease of ≥5 units without a wall motion change in 9 patients, and both a new wall motion abnormality and a marked ejection fraction decrease in 7 patients. Thus, using both criteria, radionuclide testing correctly predicted multivessel disease in 20 of 25 patients (80%) while only incorrectly predicting it in 1 patient. Combined criteria for predicting multivessel disease increased the sensitivity to 80% without changing the specificity from 92.3%.

Discussion

In recent years noninvasive techniques have been used after myocardial infarction to determine the presence of multivessel coronary artery disease and thus assess prognosis. Previous studies applied submaximal and maximal treadmill exercise testing, thallium per-

'usion imaging, and, to a limited extent, radionuclide ventriculography. In this study radionuclide ventriculography was evaluated as a prognostic method.

Our data show that with documented anterior myocardial infarction, neither the resting ejection fraction nor the ejection fraction response to exercise can be used to predict additional coronary disease beyond the distribution of the left anterior descending artery. The development of a new exercise-induced posterolateral wall motion abnormality is a specific (8 of 8, 100%), albeit insensitive (8 of 26, 31%), means of detecting multivessel disease in these patients.

For patients with previous inferior myocardial infarction however, the results differ and are more clinically useful. Both exercise ejection fraction response and wall motion analysis can discriminate single from multivessel disease. A combination of these criteria correctly predicted multivessel disease in 20 of 25 patients (80%) while incorrectly predicting it in only 1 patient with single vessel disease.

When further analysis was performed using least-square means adjusted for age, time from myocardial infarction, and use of beta-blocking drugs there was no significant change in any of the aforementioned results. Although this series was consecutive and unselected in terms of exercise radionuclide testing, the patients were entered into the study on the basis of referral for angiography. This population thus represents postinfarction patients commonly referred for cardiac catheterization and may not represent all postinfarction patients. The majority of patients in both infarct groups did not have exercise-induced angina (Table I). Inferior myocardial infarction group analysis of only the subset without angina continued to discriminate patients with multivessel disease from those with single vessel disease.

Further analysis was also performed among patients with multivessel disease after both anterior and inferior myocardial infarction. Comparisons between patients with left main, triple, and double vessel disease revealed no significant difference in exercise duration, ejection fraction, or wall motion among these 3 subgroups. Thus, we were not able to discriminate patients with left main vessel disease from those with double or triple vessel disease. The results of our study add to previously reported data on risk group stratification after myocardial infarction.

Submaximal exercise combined with radionuclide ventriculography before hospital discharge after acute myocardial infarction was recently found by Corbett et al[6] to be a sensitive means of identifying patients at high risk for a subsequent cardiac event within 6 months. Similar to results of a previous study by Pulido et al[7] but unlike those of Borer et al,[8] Corbett et al found that exercise ejection fractions varied significantly with exercise and these changes correlated with early postmyocardial infarction cardiac events. In Borer's study however, no significant change was seen between resting and exercise ejection fraction early after myocardial infarction, although a subgroup of patients with a resting ejection fraction >40%, did have a small but significant increase in ejection fraction when studied 6 to 14 months after myocardial infarction. Our patients are not comparable to the ones in these studies in that all patients had had myocardial infarction at least 8 weeks earlier. These studies do stress the problem of defining a "normal" ejection fraction response after myocardial infarction. Obviously factors such as the extent of infarction, time since infarction, and presence of additional coronary disease will determine the response to exercise in addition to other variables present in patients without infarction such as age, sex, and duration of exercise. We did not attempt to define a "normal" response but investigated whether differences in the magnitude of the exercise ejection fraction response could separate patient groups.

Our strict criteria for a new wall motion abnormality accounts for its high specificity and low sensitivity in detecting multivessel disease in both groups with myocardial infarction. This approach seems appropriate, however, in that in a patient with a prior anterior myocardial infarction, deterioration of the inferoapical segment may be secondary either to left anterior descending artery disease or to additional right coronary artery disease. Likewise, after inferior myocardial infarction, deterioration of the posterolateral segment may be secondary to disease in either the right or circumflex coronary artery. DePuey et al[9] reported results similar to ours regarding the specificity and insensitivity of wall motion abnormalities.

Shah et al,[10] in reporting their experience with wall motion on resting radionuclide ventriculograms performed during the acute setting in patients with inferior myocardial infarction, found a significantly increased incidence of wall motion abnormalities in areas remote from the infarction in a subgroup of patients with poor short-term morbidity and mortality. Although coronary arteriography was not performed, these changes were assumed to be secondary to concomitant disease in the left anterior descending artery.

Even with the self-imposed limits placed on our wall motion analysis, we believe that a new wall motion abnormality remains an important and reliable finding. Perhaps repeated exercise studies with an anterior view in patients with inferior myocardial infarction to evaluate the anterior wall, and a left lateral view in patients with anterior myocardial infarction to evaluate the inferior wall, would lead to improved sensitivity.

Postinfarction testing with thallium-201: Studies indicate that thallium-201 myocardial perfusion scanning with and without exercise stress testing is also a reliable detector of patients with multivessel disease after myocardial infarction.[11-14] However, in a study population similar to ours Rigo et al[15] examined 101 patients a minimum of 3 months after myocardial infarction using thallium-201 imaging and maximal exercise stress testing. As with our experience they were only able to detect multivessel disease in 1 of 12 patients with a prior anterior infarction, but were able to detect left anterior descending artery disease with a sensitivity of 69% in patients after inferior myocardial infarction.

Postinfarction testing using the exercise treadmill test: In patients after myocardial infarction early submaximal and late maximal treadmill stress testing

has been used to assess the presence of multivessel disease.[16–20] Castellanet et al[18] reported that after inferior myocardial infarction the S-T segment response had excellent sensitivity (87%) and specificity (90%) in detecting additional disease. Similar to our results, they found that after anterior infarction there was a reduced sensitivity (52%) with retained specificity (90%) for detecting additional disease. Paine et al[19] also showed that S-T segment changes are less sensitive in diagnosing additional coronary disease after anterior rather than after inferior myocardial infarction. In a study of 52 patients after inferior wall myocardial infarction, Miller et al[20] reported a positive exercise test result in 32 of 41 patients (78%) with multivessel disease, but also in 5 of 11 (46%) with single vessel disease.

Conclusions: Considering our data and previous reports on prognosis stratification it now seems reasonable to conclude that after inferior wall myocardial infarction, the low and high risk subgroups (or patients with single versus those with multivessel disease) can be accurately identified by exercise radionuclide ventriculography and by other analogous noninvasive tests.

In contrast, for late survivors of anterior infarction, neither exercise radionuclide ventriculography nor other noninvasive investigations differentiate patients with single or multivessel disease with sensitivity or specificity sufficient to be clinically reliable. For purposes of prognostication and intervention, coronary angiography remains the only presently reliable method to assess the extent of coronary artery disease in this patient population.

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Importance of Coronary Risk Factors in the Presence or Absence of Myocardial Ischemia

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Smoking history, systolic blood pressure, and serum cholesterol concentration were studied for their value in predicting 5-year coronary mortality in middle-aged and older Finnish men. Total experience consisted of 188 deaths from ischemic heart disease during 20,245 person-years. Initially, the men were divided into 3 groups according to the degree of myocardial ischemia: (1) previous myocardial infarction; (2) ischemic heart disease without infarction; and (3) no myocardial ischemia.

The 3 main risk factors were associated, independently of each other and of age, with the relative risk of coronary death similarly in the 3 groups, whereas their absolute impact on mortality was strong among men with ischemic heart disease and even stronger among those with a prior myocardial infarction. For example, the estimated excess coronary mortality attributable to smoking 10 to 19 cigarettes per day was 6.3 deaths per 1,000 person-years in the group with no ischemia, 14.6 in the ischemia group, and 43.1 in the infarction group.

The results suggest that secondary prevention of ischemic heart disease may be important. Screening of coronary disease among middle-aged and older men also appears justified.

Cigarette smoking, elevated blood pressure, and high concentration of serum cholesterol increase the risk of a healthy person dying from ischemic heart disease. Yet, the significance of these risk factors in persons who already have clinically manifest myocardial ischemia is still unclear.

Epidemiologic data on the predictive power of risk factors at various stages of coronary atherosclerosis and in different clinical manifestations of ischemic heart disease help clarify the etiology and pathogenesis of coronary disease. Such basic data are also needed to evaluate the potential usefulness of secondary prevention of the disease.

The aim of the present study was to compare the effects of major risk factors on coronary mortality in 3 subgroups of men: those who in screening examinations showed evidence of a prior myocardial infarction, ischemic heart disease without infarction, or no myocardial ischemia. In addition to the relative risks, the risk attributable to each factor was also considered in order to evaluate the potential benefit of preventive measures.

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Methods

Patient population: In 1959, there were 1,711 men aged 40 to 59 years from rural areas of eastern and southwestern Finland who were enrolled in a prospective study of coronary heart disease and other cardiovascular diseases.[1,2] The cohorts were followed up for deaths until 1974. The survivors were reexamined at 5-year intervals, in 1964, 1969, and 1974. The participation rate at each examination was about 95 to 98%.

Examinations: The methods used to obtain clinical and other data as well as data on resting and postexercise electrocardiogram, blood pressure, serum cholesterol concentration, and smoking habits have been described elsewhere.[1,2] All clinical data were evaluated centrally and classified according to set rules. The identification of coronary deaths was based on careful analysis of the circumstances of death.[2]

Identification of ischemic heart disease and prior myocardial infarction: The data obtained on cardiac status and the risk factors at each field examination were used to predict coronary deaths during the subsequent 5 years, independently of the data from previous or later field examinations. Therefore, the following hierarchical system was used to classify the men according to the degree of myocardial ischemia: (1) previous myocardial infarction; (2) ischemic heart disease without infarction; and (3) no myocardial ischemia. A subject was classified as having had myocardial infarction when there was a history of a verified infarction or when the resting electrocardiogram showed major Minnesota code Q or QS abnormalities (original Minnesota code[3] items 1:1, or 1:2 and 5:1,2). In the absence of infarction, a subject was classified as having myocardial ischemia when there was a history of definite or probable angina on effort[4]; when the resting electrocardiogram showed lesser Q or QS changes (items 1:2,3) or abnormalities of T-wave, atrioventricular, or

ventricular conduction (5:1–3; 6:1,2,4; 7:1,2,4), or atrial fibrillation; or when there was a horizontal or downward sloping S-T segment depression of at least 0.5 mm.[4] The majority of men (over 96% in 1959 and 1964, 89% in 1969) who did not have the foregoing symptoms or electrocardiographic signs performed an exercise test. In the group with myocardial ischemia were included those men who only had S-T segment depression in the 1-minute postexercise record.

To improve the diagnostic accuracy of the categories, subjects were excluded from the study when there were indications of pulmonary, rheumatic, or syphilitic heart disease, except when associated with major Q or QS changes. The number of excluded men varied from 13 to 32 between examinations.

Statistical analysis: The data of the 3 field examinations and of the three 5-year periods were pooled. The pooled person-years thus consist of the experience of 3 follow-up periods and refer to the length of observation from the time of the initial examination until reexamination or death, whatever the cause.

Because our aim was to demonstrate the independent predictive significance of each major risk factor, the possible confounding effects of age, geographic location, and risk factors other than the explanator had to be considered. A multifactorial analysis was therefore performed. A log-linear model[5] was formulated as follows: $\log T = \beta_\theta + \beta_1 x_1 + \ldots + \beta_k x_k + W$, where T equals the time span from entry to coronary death; $x_1, \ldots, x_k$ are the values of explanatory and confounding variables; $\beta_1, \ldots, \beta_k$ equals the values of coefficients; and W is an error variable corresponding to the exponentially distributed T. The model assumes that the intensity of coronary mortality remains constant for each 5-year period of follow-up study and that log T is a linear function of explanatory and confounding variables. Age (in years), blood pressure (in millimeters of mercury), and serum cholesterol concentration (in milligrams per 100 milliliters) were used as continua. Because systolic and diastolic pressures have closely predicted survival in a similar way in this series,[2] only the systolic pressure was included in the analysis. The following separate categories were used to evaluate the history of smoking: never smoked (control); stopped smoking; pipe or cigar smoker; cigarette smoker consuming either 1 to 9, 10 to 19, or 20 or more cigarettes per day.

Analyses were made separately for each subgroup of patients with myocardial ischemia. The risk rates for smoking categories and the risk functions of systolic pressure and serum cholesterol concentration, as estimated by the log-linear model, were standardized to coronary mortality in east Finland, the age of 55 years, and the means of other confounders in each subgroup of myocardial ischemia. The adjusted rates of risk are thus comparable between the groups in relation to age and location.

Normal deviates and confidence zones were based on the asymptomatic distribution of coefficient estimators.[5] The statistical significance over the smoking categories was tested using likelihood ratio statistics (asymptomatic chi-squared).

Measures of risk for categories or levels of risk factors were expressed in the following terms: (1) *absolute risk* is the actual rate of coronary mortality per 1,000 person-years; (2) *relative risk* is the absolute risk of the "exposed group" divided by the absolute risk of the reference group; (3) *attributable risk* is the difference between absolute risk in the exposed group and the reference group. Relative risk compares the predictive power of different levels of risk factors, and thus is suitable for etiologic appraisals, whereas attributable risk measures potential benefit of intervention.

Results

Total and coronary mortality: Altogether 440 deaths, of which 188 were caused by coronary heart disease, occurred during 20,245 person-years of follow-up study. The crude total mortality was thus 21.7 and the coronary mortality 9.3 per 1,000 person-years. In the 3 groups of patients with myocardial ischemia formed on the basis of screening examinations, the corresponding crude rates of total and coronary mortality were as follows: ischemia 15.1 (255 of 16,897) and 4.7 (79 of 16,897) in the absence of ischemia, 33.1 (125 of 3,774) and 18.5 (70 of 3,774) in ischemic heart disease but no infarction, and 109.7 (60 of 547) and 71.3 (39 of 547) deaths per 1,000 person-years in infarction, respectively. The differences reflect the drastic effect of myocardial ischemia on the risk of death from coronary disease and even from other causes, although the rates in relation to age are not exactly comparable.

Effect of smoking: Tables I to III present the predictive value of smoking habits at entry of the absolute, relative, and attributable risks of coronary death in the various groups of patients with myocardial ischemia, as adjusted by age, location, systolic pressure, and serum cholesterol concentration. There was a statistically significant increase among current cigarette smokers in both the group with no ischemia ($p = 0.003$, Table I) and the group with infarction ($p = 0.01$, Table III), whereas the variation of risk according to smoking did not quite reach statistical significance in the men with ischemic heart disease but without infarction ($p = 0.06$, Table II). No clear dose-response relation to daily cigarette consumption was evident, perhaps because of the small number of cases. Pipe or cigar smokers were excluded from the analysis of the infarction group, because no coronary death occurred during their 17 person-years of follow-up study. In the infarction and nonischemic groups, ex-smokers showed risks intermediate between those of current smokers and those of men who had never smoked, but their risks did not differ significantly from those of men who had never smoked. In the ischemia group, however, ex-smokers and men who had never smoked had similar death rates.

The risk of coronary death *attributable to smoking* was very different in the various categories of myocardial ischemia. For example, the attributable risk of coronary death per 1,000 person-years in men consuming 20 or more cigarettes per day was 4.1 in men without myocardial ischemia, 12.1 in men with ischemia but no infarction, and as high as 70.1 in men with a prior infarction. These rates show the great significance of smoking in the presence of myocardial ischemia when the inherent mortality is high.

Effects of systolic pressure and serum cholesterol: Coronary mortality as a log-linear function of systolic pressure and serum cholesterol concentration in the various subgroups of patients with myocardial ischemia at entry is presented in Figures 1 and 2. The functions have been standardized to the mortality of men aged 55 years in east Finland, being mutually comparable. The relation of systolic pressure and serum cholesterol to coronary mortality proved similar in the

subgroups, as shown by the parallel slopes of the lines in both Figures 1 and 2. However, the association between the risk factors and mortality was statistically significant only for systolic pressure in men with myocardial ischemia but no infarction ($p = 0.01$) and for serum cholesterol in men without ischemia and in those with ischemia but no infarction ($p = 0.02$), whereas the findings remained nonsignificant ($p = 0.1$ to 0.3) in the other groups.

As with smoking, the absolute importance of systolic pressure or serum cholesterol was far greater in men with myocardial ischemia at entry, particularly those with a prior infarction, than in men with no evidence of ischemia. On the basis of the risk functions presented in Figures 1 and 2 and of the means and standard deviations shown in Table IV, the risks attributable to given changes of systolic pressure or serum cholesterol concentration can be estimated. For example, if systolic

TABLE I Absolute, Attributable, and Relative Risk of Coronary Death According to Smoking History in Men Without Myocardial Ischemia at Entry*

	Smoking History						
				Cigarettes/Day			
	Never	Stopped	Pipe or Cigar	1–9	10–19	≥20	Total
Deaths (n)	5	15	3	9	26	21	79
Man-years	3,239	3,752	436	1,881	3,600	3,989	16,897
Absolute risk (deaths/1,000 man-years)	1.5	3.3	7.1	4.7	7.8	5.6	4.1
Attributable risk (deaths/1,000 man-years)	...	1.8	5.6	3.2	6.3	4.1	...
Relative risk	1.0	2.2	4.7	3.1	5.2	3.7	...
Normal deviate	...	1.48	2.12	2.02	3.25	2.60	...
p value	...	0.1	0.03	0.04	0.001	0.01	...

Chi-square = 18.08 (df = 5; p = 0.003).
* Mortality rates are estimated by the log-linear model and standardized to the mortality of men aged 55 years in east Finland; age, location, systolic pressure, and serum cholesterol concentration allowed.

TABLE II Absolute, Attributable, and Relative Risk of Coronary Death According to Smoking History in Men With Ischemic Heart Disease But No Prior Infarction at Entry*

	Smoking History						
				Cigarettes/Day			
	Never	Stopped	Pipe or Cigar	1–9	10–19	20 or More	Total
Deaths (n)	7	12	1	6	21	23	70
Man-years	727	961	97	398	666	925	3774
Absolute risk (deaths/1,000 man-years)	11.4	11.1	5.4	16.1	26.0	23.5	16.0
Attributable risk (deaths/1,000 man-years)	...	−0.3	−6.0	4.7	14.6	12.1	...
Relative risk	1.0	1.0	0.5	1.4	2.3	2.1	...
Normal deviate	...	−0.06	−0.69	0.62	1.84	1.64	...
p value	...	1.0	0.5	0.5	0.06	0.1	...

Chi-square = 10.39 (df = 5; p = 0.06)
* Mortality rates are estimated by the log-linear model and standardized to the mortality of men aged 55 years in east Finland; age, location, systolic pressure and serum cholesterol concentration allowed.

TABLE III Absolute, Attributable, and Relative Risk of Coronary Death According to Smoking History in Men With a Previous Myocardial Infarction*

	Smoking History					
			Cigarettes/Day			
	Never	Stopped	1–9	10–19	20 or More	Total
Deaths (n)	1	12	9	7	10	39
Man-years	92.5	163	55.3	114	122	547
Absolute risk (deaths/1,000 man-years)	9.7	71.2	151.1	52.8	79.8	56.0
Attributable risk (deaths/1,000 man-years)	...	61.5	140.4	43.1	70.1	...
Relative risk	1.0	7.4	15.5	5.5	8.2	...
Normal deviate	...	1.91	2.58	1.57	1.97	...
p value	...	0.06	0.01	0.1	0.05	...

Chi-square = 12.43 (df = 4; p = 0.01)
* Mortality rates are estimated by the log-linear model and standardized to the mortality of men aged 55 in east Finland; age, location, systolic pressure, and serum cholesterol concentration allowed. Pure pipe and cigar smokers are excluded.

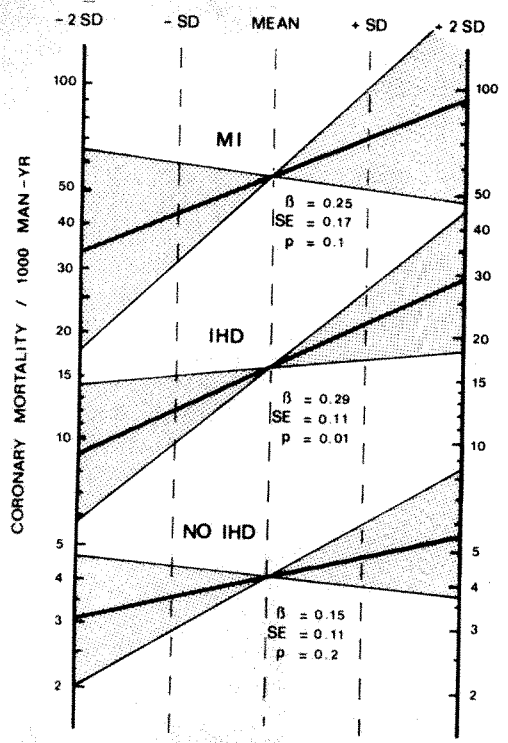

FIGURE 1. Five-year coronary mortality ±95% confidence zone as a function of systolic pressure in men with a prior myocardial infarction (MI), ischemic heart disease (IHD) without infarction, and no evidence of myocardial ischemia (NO IHD) at entry. Mortality rates are estimated by the log-linear model and standardized to the mortality of men aged 55 years in east Finland in relation to age, location, smoking history, and serum cholesterol levels. The means and standard deviations (SD) of systolic pressure are given in Table IV. β = value of coefficient; SE = standard error of β.

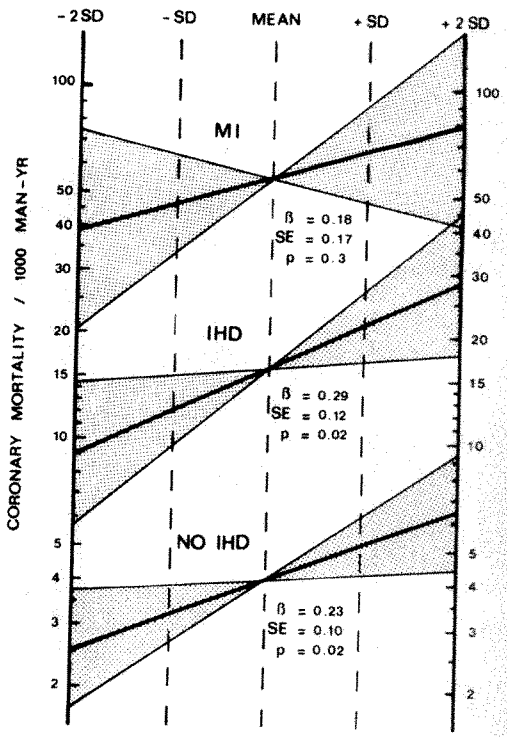

FIGURE 2. Five-year coronary mortality ±95% confidence zone as a function of serum cholesterol concentration in men with a prior myocardial infarction (MI), ischemic heart disease (IHD) without infarction, and no evidence of myocardial ischemia (NO IHD) at entry. Mortality rates are estimated by the log-linear model and standardized to the mortality of men aged 55 in east Finland in relation to age, location, smoking history, and systolic pressure. The means and standard deviations (SD) of serum cholesterol are given in Table IV. β = value of coefficient; SE = standard error of β.

pressure is elevated 30 mm Hg above the mean, the estimate for 5-year coronary mortality increases from 4.1 to 5.2 deaths per 1,000 person-years in men without myocardial ischemia, from 16 to 23 in men with ischemia but no infarction, and from 56 to 73 in men with a prior infarction. Accordingly, an increase in serum cholesterol by 50 mg/100 ml above the mean produces an additional 1.0 coronary death per 1,000 person-years in men without myocardial ischemia, 4.5 deaths in men with ischemia but no infarction, and 9.1 deaths in men with infarction. These estimates, however, are only approximate because of random variation in risk functions.

Additional analyses: The effects of smoking, systolic blood pressure, and serum cholesterol on the adjusted coronary mortality were also separately analyzed for each of the 5-year periods. The results were similar to those in the pooled series except that serum cholesterol predicted mortality during the second and third period only. However, the numbers were too small for definite conclusions to be drawn. Neither did the experience prove sufficient to test the significance of the interactions between the risk factors.

Discussion

Main observations: Smoking, systolic pressure, and serum cholesterol concentration, the classic risk factors of coronary death, were operative even in men who already had clinically manifest myocardial ischemia. Three separate groups of men were analyzed: those with prior myocardial infarction, those with ischemic heart disease but no infarction, and those with no evidence of ischemia. Analysis showed that the risk factors predicted the *relative* likelihood of death from coronary heart disease similarly within the 3 groups. However, the *absolute* impact of these factors on mortality was strong in the presence of myocardial ischemia, especially among men who had had an infarction.

TABLE IV Mean ± Standard Deviation (SD) of Systolic Pressure, Serum Cholesterol Concentration, and Age With 3 Screening Examinations Pooled

	No Ischemia		Ischemic Heart Disease		Myocardial Infarction	
Variable	Mean	SD	Mean	SD	Mean	SD
Systolic pressure (mm Hg)	140.9	19.9	152.2	25.6	155.7	28.6
Serum cholesterol (mg/100 ml)	267.4	53.6	273.4	58.0	278.9	59.2
Age (yr)	54.3	6.6	57.6	6.4	59.3	6.3

Nature of the study: The subjects were middle-aged and older men from rural areas of Finland and were mainly small farmers. The participation rate was exceptionally high, and the follow-up period covered all subsequent deaths. Because ischemic heart disease is very common among Finnish men, the number of cases was sufficient to demonstrate the main findings reliably. The applicability of these findings to other populations has to be shown.

The study was based on *screening examinations of a nonselected population.* Our diagnostic entities of myocardial infarction and ischemic heart disease may thus differ from clinical series of patients, which probably, on the average, contain more severe cases. The predictive value of initial measurements in a prospective study may be blurred with time during a very long follow-up period. Data on risk factors and myocardial ischemia were therefore updated at intervals of 5 years, in order to shorten the time span from the examination to the end-point. The total experience thus consisted of 3 consecutive follow-up periods of the same cohort. In principle, a single 5-year follow-up study of a 3-fold population with the same age structure would have given similar information.

Risk factors and survival in ischemic heart disease: In several studies[6–9] cigarette smoking proved to significantly worsen the long-term prognosis of patients who survive after myocardial infarction. Serum cholesterol concentration also has an effect on survival after recovery from infarction,[10] whereas blood pressure is less important.[11] In the present study, all 3 risk factors predicted the survival of men who had already had a myocardial infarction, although the association was statistically significant for smoking only. In our analysis the follow-up period did not start at the time of the infarction. Because the prognosis of the survivors improves with time[12] and myocardial infarction itself may affect the level of risk factors, at least during hospitalization and possibly also later, our results cannot be directly compared with those of others.

So far, little research has been done on the significance of risk factors in men with angina pectoris or minor electrocardiographic findings of ischemic heart disease. In the Whitehall study[13] of British male civil servants, the main risk factors predicted 5-year coronary mortality even during early myocardial ischemia. Yet, subjects with a prior myocardial infarction and mild ischemic heart disease were not analyzed separately. Earlier, the Health Insurance Plan of Greater New York had reported differences in prognosis related to cigarette smoking, blood pressure, and serum cholesterol levels among men with newly diagnosed angina,[14] but the cases were too few to permit confident conclusions. Our findings confirm the significance of classic risk factors in early ischemic heart disease.

The view that the association between major risk factors and ischemic heart disease is causal in nature is supported by its intensity, coherence, consistency between various populations, and dose-response relation.[15] Our epidemiologic findings indicate that smoking, blood pressure, and serum cholesterol are continously involved with development and progression of coronary disease at any stage.

Implications for prevention: Secondary prevention of ischemic heart disease by intervention against risk factors has generally been considered reasonable,[16] although its benefits are less well established than those of primary prevention. Our finding that the risk of coronary death attributable to smoking, systolic pressure, and serum cholesterol in men with clinically manifest ischemic heart disease was much greater than the risk in men without evidence of myocardial ischemia suggests that secondary prevention is of primary importance. However, that the reduction of risk factor levels improves the prognosis remains unconfirmed, even though a favorable effect, such as that achieved through diet, has been suggested.[17–19] Our results also justify the institution of screening for coronary heart disease among middle-aged and older men with subsequent intervention against risk factors.

Our series is too small to demonstrate reliably quantitative relations between various levels of risk factors and survival in subjects with ischemic heart disease. Further longitudinal studies are therefore needed.

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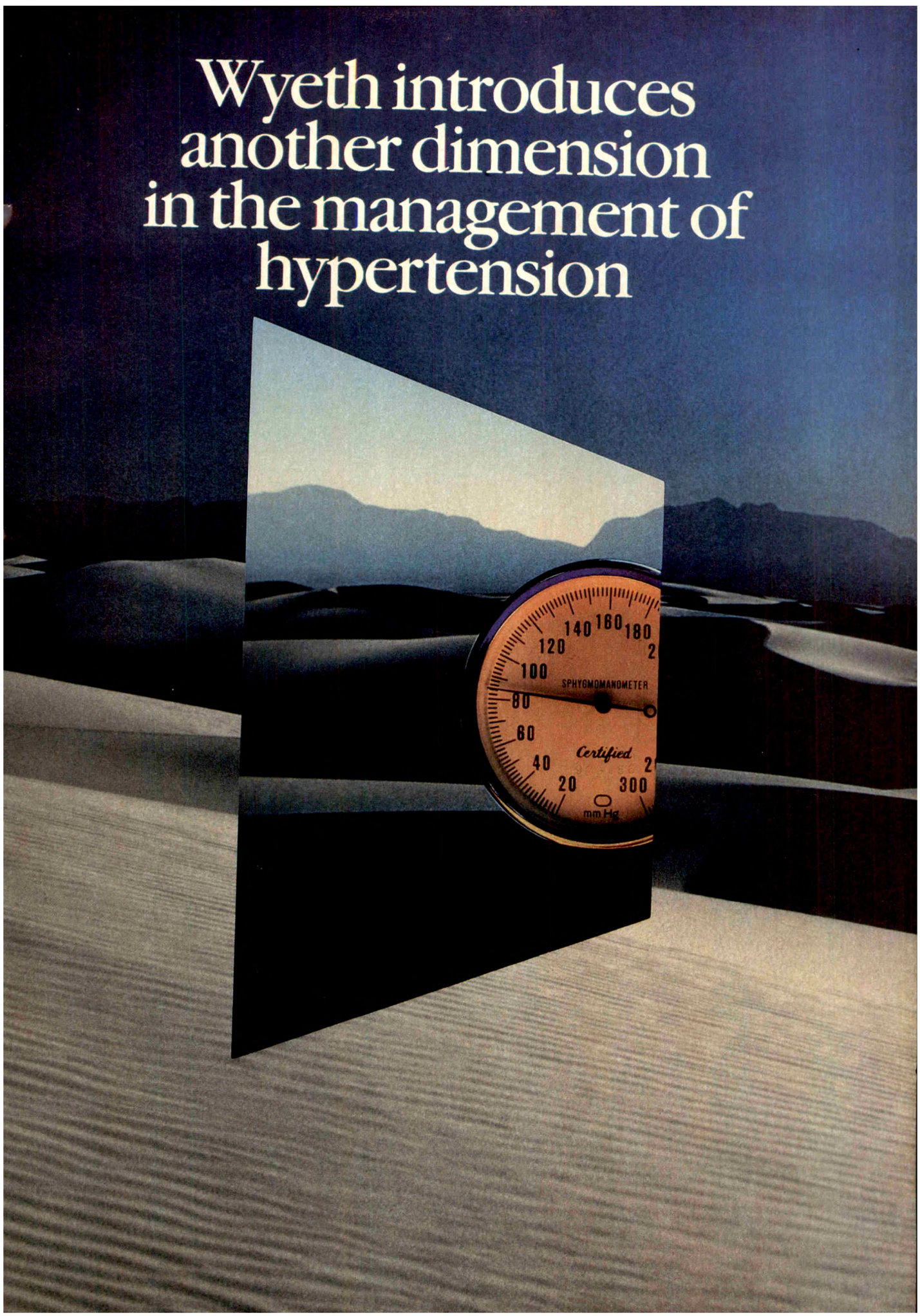
Wyeth introduces another dimension in the management of hypertension



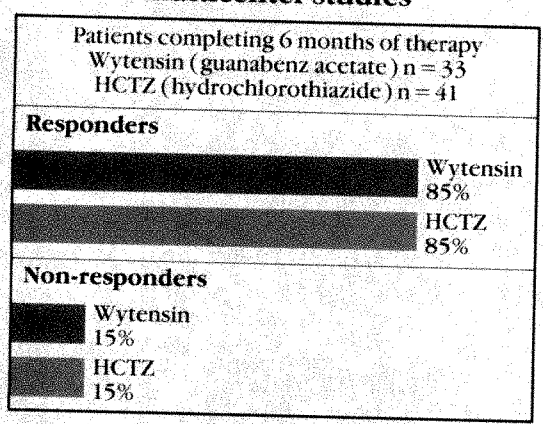
In clinical trials to date:

no potassium depletion
no volume depletion
no hyperlipidemia
no hyperuricemia
no hypercalcemia
no acid-base disturbances
no increased renin activity
no increased catecholamines
no azotemia
no hyperglycemia

Wyeth

Another dimension of management beyond the scope of diuretics

Highly effective in double-blind, multicenter studies



Important homeostatic advantages

	Wytensin	HCTZ
potassium	—	↓
renin	—	↑
glucose	—	↑
serum cholesterol	↓	↑
chloride	—	↓
uric acid	—	↑
calcium	—	↑
BUN	—	↑

Wytensin® did not induce long-term cardiovascular risk factors.[1]
Unlike diuretics, Wytensin can be used over the long-term without inducing atherogenic potential risk factors such as hyperlipidemia and hyperglycemia or arrhythmic risk factors such as hypokalemia. With Wytensin therapy a small decrease in heart rate and weight has been observed.

Wytensin® side effects are usually mild and transient.
Although dry mouth and/or drowsiness were the most frequently noted side effects, these subjective complaints usually diminished or disappeared over time. Only 9% of patients discontinued therapy due to drowsiness or dry mouth.
About one third of patients who started Wytensin therapy with 8 mg twice daily experienced these side effects, but starting with 4 mg b.i.d.—the recommended starting dose—reduced both the incidence of these side effects and the consequent dropout rate. In all studies to date, discontinuance of therapy for all side effects occurred in about 15% of patients.

Wytensin® may lower the price the patient pays for therapy.
Because Wytensin did not induce electrolyte and metabolic imbalance, it may save patients trouble and money. A Wytensin prescription reduces the need for frequent laboratory testing as well as for K-sparing agents or K supplements and other agents that frequently cost more than diuretics alone.

New

WyTensin®

(guanabenz acetate)

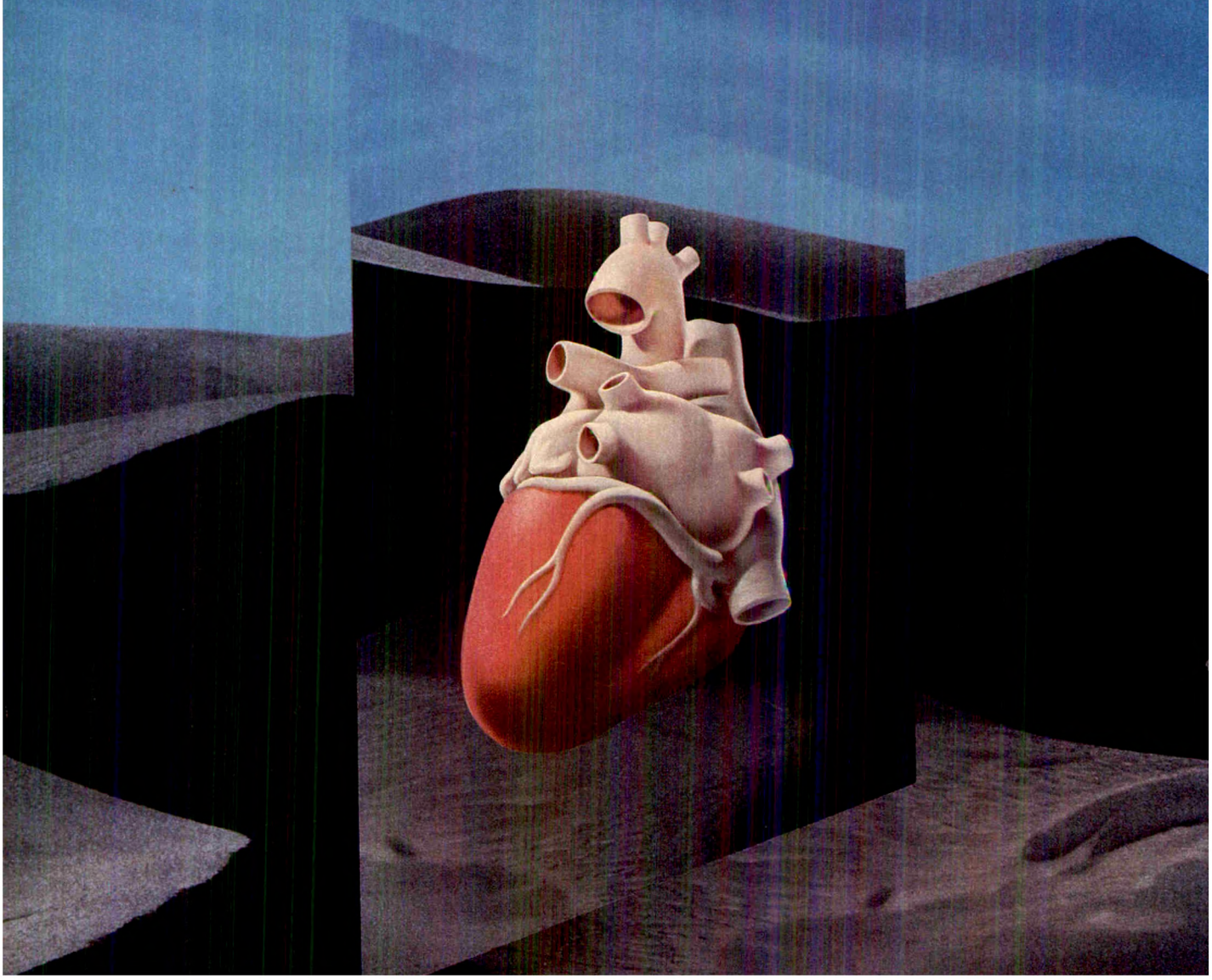
4 mg b.i.d.

Initial monotherapy in hypertension

e important information on last page.

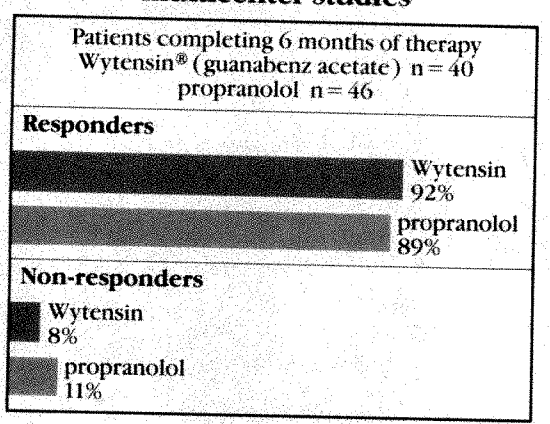
In clinical trials to date:

no contraindications except hypersensitivity
no decrease in cardiac output
no increase in peripheral resistance
no decrease in glomerular filtration rate
no decrease in exercise tolerance
no hyperkalemia
no masking of hypoglycemia
no weight gain
no memory loss
no increase in serum cholesterol
no increase in plasma catecholamines



Another dimension of management beyond the scope of beta-blockers

Highly effective in double-blind, multicenter studies



Important homeostatic advantages

	Wytensin	propranolol
potassium	—	↑
serum cholesterol	↓	—
cardiac output	—	↓
glomerular filtration rate	—	↓
peripheral resistance	↓	↑
exercise tolerance	—	↓
plasma catecholamines	↓	↑

Wytensin® lacks the risks of beta-blockade.
Wytensin® is less problematic than beta-blockers, which are contraindicated in many patients and must be used with caution in many others. For instance, exercise intolerance, nightmares, and memory failure can be problems with beta-blockers, and in many black and/or elderly patients, beta-blockade is ineffective.

Wytensin® side effects are usually mild and transient.
The subjective complaints of drowsiness and dry mouth were the most frequently noted side effects and usually diminished or disappeared over time. During initial therapy, patients should be cautioned against driving automobiles or operating dangerous machinery.

Wytensin® can be used in a broader spectrum of hypertensives.
In contrast to beta-blockers, Wytensin has no contraindications except hypersensitivity and is effective regardless of the aging process or racial factors. And, unlike beta-blockers, Wytensin causes a slight decrease in serum cholesterol and maintains potassium balance. Moreover, Wytensin does not cause clinically significant bradycardia or decreased cardiac output. There is no stimulation of vasopressor mechanisms.[2]

New

WyTensin®

(guanabenz acetate)

4 mg b.i.d.

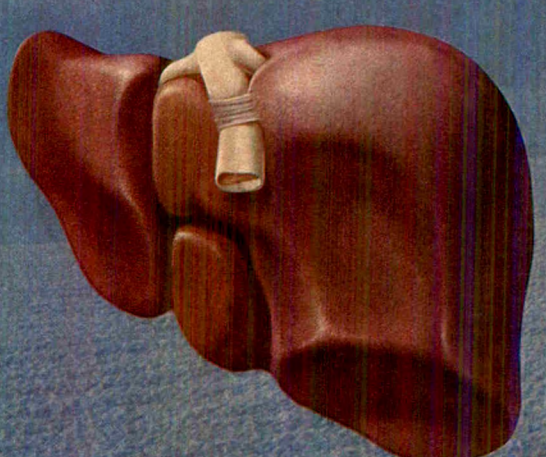
Initial monotherapy in hypertension

See important information on last page.

In clinical trials to date:

no sodium retention
no weight gain
no decrease in GFR

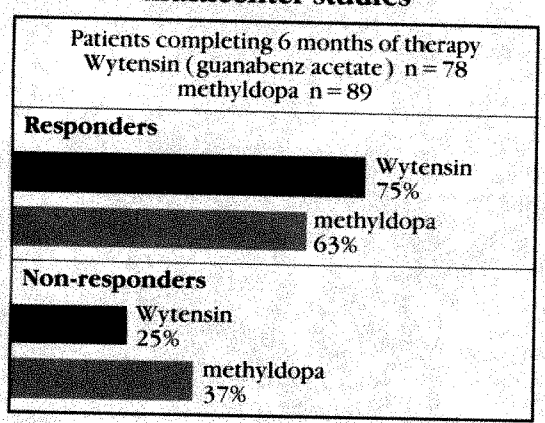
no immunological disturbances
no liver damage
no hemolytic anemia



Wyeth

Another dimension of management beyond the scope of methyldopa

Highly effective in double-blind, multicenter studies



Important homeostatic advantages

	Wytensin	methyldopa
sodium excretion	—	↓
plasma volume	—	↑
weight	↓	↑
glomerular filtration rate	—	↓

Wytensin® does not produce sodium retention or volume expansion.[3]
Methyldopa causes sodium retention and volume expansion with consequent development of drug tolerance. In contrast, drug tolerance has not developed with Wytensin probably because it does not induce retention of sodium and body fluid.

Wytensin® is virtually free of serious adverse reactions.
Unlike methyldopa, Wytensin does not produce immunological blood or liver toxicity or produce a positive Coombs' test. Wytensin also lacks the relatively high incidence of sexual dysfunction or mental depression seen with methyldopa.

Wytensin® side effects are often transient or avoidable.
Patients may experience drowsiness and dry mouth early during Wytensin therapy, but these effects are mostly mild, especially when the initial dosage is 4 mg b.i.d., with the second dose administered **h.s.**

New

WyTensin®

(guanabenz acetate)

4 mg b.i.d.

Initial monotherapy in hypertension

ee important information on last page.

Initial monotherapy in hypertension

New Wytensin® (guanabenz acetate) 4 mg b.i.d.

More than 1,400 patients evaluated

No sodium retention

No electrolyte or metabolic risk factors

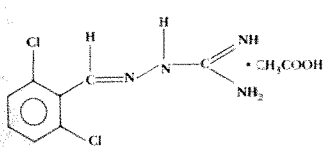
A favorable therapeutic index

Convenient, compliance-enhancing b.i.d. dosage

No contraindications except hypersensitivity

Description

Wytensin (guanabenz acetate), an antihypertensive agent for oral administration, is an aminoguanidine derivative, 2,6-dichlorobenzylideneaminoguanidine acetate, and its structural formula is:



It is an odorless, white to off-white, crystalline substance, sparingly soluble in water and soluble in alcohol, with a molecular weight of 291.14. Each tablet of Wytensin is equivalent to 4 mg or 8 mg of free guanabenz base.

Wytensin is available as 4 or 8 mg tablets for oral administration.

Clinical Pharmacology

Wytensin is an orally active central alpha-2 adrenergic agonist. Its antihypertensive action appears to be mediated via stimulation of central alpha adrenergic receptors, resulting in a decrease of sympathetic outflow from the brain at the bulbar level to the peripheral circulatory system.

PHARMACOKINETICS

In human studies, about 75% of an orally administered dose of Wytensin is absorbed and metabolized with less than 1% of unchanged drug recovered from the urine. Peak plasma concentrations of unchanged drug occur between two and five hours after a single oral dose. The average half-life for Wytensin is about 6 hours. The site or sites of metabolism of Wytensin and the consequences of renal or hepatic insufficiency on excretion of Wytensin or its metabolites have not been determined. The effect of meals on the absorption of Wytensin has not been studied.

PHARMACODYNAMICS

The onset of the antihypertensive action of Wytensin begins within 60 minutes after a single oral dose and reaches a peak effect within two to four hours. The effect of an acute single dose is reduced appreciably six to eight hours after administration, and blood pressure approaches baseline values within 12 hours of administration.

The acute antihypertensive effect of Wytensin occurs without major changes in peripheral resistance, but its chronic effect appears to be a decrease in peripheral resistance. A decrease in blood pressure is seen in both the supine and standing positions without alterations of normal postural mechanisms, so that postural hypotension has not been observed. Wytensin decreases pulse rate by about 5 beats per minute. Cardiac output and left ventricular ejection fraction are unchanged during long-term therapy.

With effective control of blood pressure in hypertensive patients, Wytensin has not demonstrated any significant effect on glomerular filtration rate, renal blood flow, renal sodium or potassium excretion, renal concentrating ability, body fluid volume, or body weight. In clinical trials of six to thirty months, hypertensive patients whose blood pressure was controlled with Wytensin lost one to four pounds of body weight. The mechanism of this weight loss has not been established. Tolerance to the antihypertensive effect of Wytensin has not been observed.

During long-term administration of Wytensin, there is a small decrease in serum cholesterol and total triglycerides without any change in the high-density lipoprotein fraction. Plasma norepinephrine, serum dopamine beta-hydroxylase, and plasma renin activity are decreased during chronic administration of Wytensin. No changes in serum electrolytes, uric acid, blood urea nitrogen, calcium, or glucose have been observed.

Wytensin and hydrochlorothiazide have been shown to have at least partially additive effects in patients not responding adequately to either drug alone.

Indications and Usage

Wytensin is indicated in the treatment of hypertension. It may be employed alone or in combination with a thiazide diuretic.

Contraindication

Wytensin is contraindicated in patients with a known sensitivity to the drug.

Precautions

1. Sedation: Wytensin causes sedation or drowsiness in a large fraction of patients. When Wytensin is used with centrally active depressants, such as phenothiazines, barbiturates, and benzodiazepines, the potential for additive sedative effects should be considered.

2. Patients with vascular insufficiency: Wytensin, like other antihypertensive agents, should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or severe hepatic or renal failure.

3. Rebound: Sudden cessation of therapy with central alpha agonists like Wytensin may rarely result in "overshoot" hypertension and more commonly produces an increase in serum catecholamines and subjective symptomatology.

INFORMATION FOR PATIENTS

Patients who receive Wytensin should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

LABORATORY TESTS

In clinical trials, no clinically significant laboratory test abnormalities were identified during either acute or chronic therapy with Wytensin. Tests carried out included CBC, urinalysis, electrolytes, SGOT, bilirubin, alkaline phosphatase, uric acid, BUN, creatinine, glucose, calcium, phosphorus, total protein, and Coombs' test. During long-term administration of Wytensin, there was a small decrease in serum cholesterol and total triglycerides without any change in the high-density lipoprotein fraction. In rare instances an occasional nonprogressive increase in liver enzymes has been observed. However, no clinical evidence of hepatic disease has been found.

DRUG INTERACTIONS

Wytensin has not been demonstrated to cause any drug interactions when administered with other drugs, such as digitalis, diuretics, analgesics, anxiolytics, and antiinflammatory or antiinfective agents, in clinical trials. However, the potential for increased sedation when Wytensin is administered concomitantly with CNS depressant drugs should be noted.

DRUG/LABORATORY TEST INTERACTIONS

No laboratory test abnormalities were identified with the use of Wytensin.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

No evidence of carcinogenic potential emerged in rats during a two-year oral study with Wytensin at doses up to 9.5 mg/kg/day, i.e., about 10 times the maximum recommended human dose. In the Salmonella microsome mutagenicity (Ames) test system, Wytensin at 200-500 mcg per plate or at 30-50 mcg/ml in suspension gave dose-related increases in the number of mutants in one (TA 1537) of five *Salmonella typhimurium* strains with or without inclusion of rat liver microsomes. No mutagenic activity was seen at doses up to those which inhibit growth in the eukaryotic microorganism, *Schizosaccharomyces pombe*, or in Chinese hamster ovary cells at doses up to those which were lethal to the cells in culture. In another eukaryotic system, *Saccharomyces cerevisiae*, Wytensin produced no activity in an assay measuring induction of repairable DNA damage. Reproductive studies showed a decreased pregnancy rate in rats administered high oral doses (9.6 mg/kg) of Wytensin, suggesting an impairment of fertility. The fertility of treated males (9.6 mg/kg) may also have been affected, as suggested by the decreased pregnancy rate of their mates, even though the females received Wytensin only during the last third of pregnancy.

PREGNANCY

Pregnancy Category C

WYTENSIN MAY HAVE ADVERSE EFFECTS ON THE FETUS WHEN ADMINISTERED TO PREGNANT WOMEN. A teratology study in mice has indicated a possible increase in skeletal abnormalities when Wytensin is given orally at doses of 3 to 6 times the maximum recommended human dose of 1.0 mg/kg. These abnormalities, principally costal and vertebral, were not noted in similar studies in rats and rabbits. However, increased fetal loss has been observed after oral Wytensin administration to pregnant rats (14 mg/kg) and rabbits (20 mg/kg). Reproductive studies of Wytensin in rats have shown slightly decreased live-birth indices, decreased fetal survival rate, and decreased pup body weight at oral doses of 6.4 and 9.6 mg/kg. There are no adequate, well-controlled studies in pregnant women. Wytensin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Because no information is available on the excretion of Wytensin in human milk, it should not be administered to nursing mothers.

PEDIATRIC USE

The safety and effectiveness of Wytensin in children less than 12 years of age have not been demonstrated. Therefore, its use in this age group cannot be recommended at this time.

Adverse Reactions

The incidence of adverse effects has been ascertained from controlled clinical studies conducted in the United States and is based on data from 859 patients who received Wytensin for up to 3 years. There is some evidence that the side effects are dose-related.

The following table shows the incidence of adverse effects occurring in at least 5% of patients in a study comparing Wytensin to placebo, at a starting dose of 8 mg b.i.d.

Adverse Effect	Placebo (%) n = 102	Wytensin (%) n = 109
Dry mouth	7	28
Drowsiness or sedation	12	39
Dizziness	7	17
Weakness	7	10
Headache	6	5

In other controlled clinical trials at the starting dose of 16 mg/day in 476 patients, the incidence of dry mouth was slightly higher (38%) and that of dizziness was slightly lower (12%), but the incidence of the most frequent adverse effects was similar to the placebo-controlled trial. Although these side effects were not serious, they led to discontinuation of treatment about 15% of the time. In more recent studies using an initial dose of 8 mg/day in 274 patients, the incidence of drowsiness or sedation was lower, about 20%.

Other adverse effects were reported during clinical trials with Wytensin but are not clearly distinguishable from placebo effects and occurred with a frequency of 3% or less:

Cardiovascular—chest pain, edema, arrhythmias, palpitations.
Gastrointestinal—nausea, epigastric pain, diarrhea, vomiting, constipation, abdominal discomfort.
Central nervous system—anxiety, ataxia, depression, sleep disturbances.
ENT disorders—nasal congestion.
Eye disorders—blurring of vision.
Musculoskeletal—aches in extremities, muscle aches.
Respiratory—dyspnea.
Dermatologic—rash, pruritus.
Urogenital—urinary frequency, disturbances of sexual function.
Other—gynecomastia, taste disorders.

Drug Abuse and Dependence

No reported dependence or abuse has been associated with the administration of Wytensin.

Overdosage

Accidental ingestion of Wytensin caused hypotension, somnolence, lethargy, irritability, miosis, and bradycardia in two children aged one and three years. Gastric lavage and administration of pressor substances, fluids, and oral activated charcoal resulted in complete and uneventful recovery within 12 hours in both patients.

Since experience with accidental overdosage is limited, the suggested treatment is mainly supportive while the drug is being eliminated from the body and until the patient is no longer symptomatic. Vital signs and fluid balance should be carefully monitored. An adequate airway should be maintained and, if indicated, assisted respiration instituted. There are no data available on the dialyzability of Wytensin.

Dosage and Administration

Dosage with Wytensin should be individualized. A starting dose of 4 mg twice a day is recommended, whether Wytensin is used alone or with a thiazide diuretic. Dosage may be increased in increments of 4 to 8 mg per day every one to two weeks, depending on the patient's response. The maximum dose studied to date has been 32 mg twice daily, but doses as high as this are rarely needed.

How Supplied

Wytensin® (guanabenz acetate) Tablets, Wyeth®, are available in the following dosage strengths:

4 mg, NDC 0008-0073, white, round tablet marked "WYETH" and "73", in bottles of 100.

8 mg, NDC 0008-0074, white, round, scored tablet marked "WYETH" and "74", in bottles of 100.

Keep bottles of Wytensin Tablets tightly closed.
Dispense in tight containers.
Protect from light.

Issued August 17, 1982

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Cold Pressor Thallium-201 Myocardial Scintigraphy in the Diagnosis of Coronary Artery Disease

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Thallium-201 myocardial scintigraphy was performed during cold pressor stimulation in 36 patients aged 37 to 69 years. Thirty-one patients had coronary artery disease and 5 patients did not, as confirmed by coronary cineangiography. Thallium-201 (1.5 to 2 mCi) was injected at 30 seconds of the cold pressor stimulation. The product of systolic pressure × heart rate increased from a baseline of 77.4 ± 16 (standard deviation [SD]) to 103.6 ± 17 at 30 seconds of the cold pressor test ($p < 0.0005$). Transient perfusion deficits developed in 24 of 31 patients with coronary artery disease (sensitivity 77%), and all 5 patients without coronary artery disease had normal scintigrams. The sensitivity in detecting coronary artery disease was 40% in patients with 1 vessel disease, 91% in patients with 2 vessel disease, and 100% in patients with 3 vessel disease. Exercise electrocardiograms (available in 29 of 36 patients) were positive for ischemia in 18 of 24 patients with coronary artery disease and in 1 of 5 patients without coronary artery disease (sensitivity 75% and specificity <80%). Exercise thallium-201 scintigrams, obtained in 16 patients, were positive in 11 patients with coronary artery disease and positive cold pressor thallium-201 scintigrams. Five patients without coronary artery disease and with normal cold pressor thallium-201 scintigrams had normal exercise thallium-201 scintigrams. Coronary cineangiography performed during cold pressor stimulation in 6 patients who had positive cold pressor and exercise thallium-201 scintigrams did not show coronary spasm. Our data indicate that cold pressor thallium-201 scintigraphy offers promise as a noninvasive test in the diagnosis of coronary artery disease and may be used in patients in whom exercise testing is not feasible.

Thallium-201 myocardial scintigraphy with exercise has proved a valuable noninvasive technique in the evaluation of myocardial perfusion in patients with coronary artery disease.[1] Many sick and debilitated patients, however, are unable to perform the exercise needed for the test, and some have symptoms that are not related to exercise. The cold pressor test results in a rapid increase in blood pressure and induces abnormalities in left ventricular function in patients with coronary artery disease.[2,3] In the present study, cold pressor stimulation was examined for the first time as an alternative to the standard exercise stress test in the scintigraphic evaluation of myocardial perfusion.

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Methods

Patient population: The study group consisted of 36 patients (aged 37 to 69 years) whose coronary anatomy had been studied by coronary angiography. The patients were selected from a population being evaluated for chest pain syndromes and for possible coronary artery bypass surgery. Typical angina pectoris, brought on by exertion and relieved by rest and nitrates, was present in 30 patients. Six patients presented with chest pain that was atypical either in location or in its relation to exertion and nitrates. The duration of symptoms ranged from 1 to 11 years. Thirty-one patients were taking nitrates for relief of chest pain. Five patients were being treated with propranolol (40 to 180 mg daily) and 4 patients were taking digoxin (0.25 mg daily) and diuretics at the time of the study. Five patients had evidence of previous myocardial infarction, transmural in 2 patients and nontransmural in 3. Seven patients had ventricular arrhythmias (premature ventricular contractions) and nonspecific ST-T wave changes. There was evidence of cardiomegaly in 3 patients. All patients underwent standard left heart catheterization, and coronary

cineangiograms were obtained in multiple projections. Left ventricular and coronary cineangiograms were interpreted by a single experienced observer. Coronary artery disease was diagnosed when ≥50% luminal diameter narrowing was observed in at least 1 major coronary artery. The interpretation of coronary angiograms was based on the observer's visual estimate of the degree of luminal narrowing. Thirty-one patients had significant coronary artery disease. Triple vessel coronary artery disease was present in 10 patients, double vessel disease in 11 patients, and single vessel disease in 10 patients. In the remaining 5 patients, coronary angiograms were read as normal based on no disease in 3 patients and <50% luminal diameter narrowing of 1 of the major vessels in 2 patients. Greater than 50% narrowing of the left main coronary artery was present in 2 patients with triple vessel disease. Seven patients with triple vessel disease had areas of ventricular wall motion abnormality, and small discrete left ventricular aneurysms were present in 2 of these 7 patients. Two patients with double vessel disease also had areas of left ventricular wall motion abnormality. The left ventricular ejection fraction of 5 patients (4 with triple vessel and 1 with double vessel disease) was depressed and ranged from 35 to 45%. The resting left ventricular end-diastolic pressure in these 5 patients was abnormally elevated. In 5 patients, the left ventricular ejection fraction was mildly depressed, ranging from 45 to 55%, and the remaining 26 patients had a normal resting ejection fraction.

Twenty-nine patients (24 with and 5 without coronary artery disease) were able to complete a symptom-limited maximal exercise stress test using Bruce's[4] multistage treadmill protocol. The patient's heart rate, blood pressure, and electrocardiogram (modified V_5 electrode) were monitored throughout the exercise. In 13 patients, the exercise stress test was carried out at the time of hospitalization for cardiac catheterization. In the remaining 16 the test had been performed for the evaluation of chest pain within the 6 months before hospitalization. Seven patients did not have an exercise stress test, either because of an unstable clinical state (4 patients) or because of severe peripheral vascular disease (3 patients). All exercise stress test electrocardiograms were interpreted by a single experienced observer without knowledge of the patients' angiographic or scintigraphic data. Exercise stress test was interpreted as positive when >1 mm S-T segment depression was observed in the exercise electrocardiogram.

Cold pressor thallium-201 scintigraphy: All patients underwent thallium-201 myocardial scintigraphy after the cold pressor test. After the baseline electrocardiogram and blood pressure were recorded, the patient's one hand was suddenly immersed up to the level of the styloid process in a bucket of ice water (temperature 0 to 2°C) for 2 to 3 minutes. The electrocardiogram and blood pressure were monitored continuously. Thallium-201 (1 to 2 mCi) was injected intravenously through a previously established intravenous line between 30 and 60 seconds of the cold pressor test. This time of injection was chosen because maximal changes in heart rate and blood pressure occurred at 30 seconds of cold exposure in all patients. In addition, this time of injection allowed the maximal uptake of thallium-201 by the myocardium to occur while the patient was still under cold pressor challenge. Imaging was begun within 5 to 10 minutes of the termination of the cold pressor test. An Ohio Nuclear Series 120 Gamma Camera and a high resolution collimator were used for imaging. Polaroid scintiphotographs with counts of 300,000 to 400,000 were obtained in the anterior, 45° left anterior oblique, and left lateral views. Data were also recorded on magnetic tape for subsequent analysis on a PDP-11 digital computer. Follow-up thallium-201 scintigrams were obtained in the same projections 4 hours after the initial scintigrams. Image processing and interpretations were carried out as previously described.[5] All interpretations were based on polaroid scintiphotographs. Computer-processed images were used for further confirmation of the results. Briefly, thallium-201 scintigrams were interpreted as abnormal when a discrete area of decreased or absent activity was noted. Partial or complete resolution of the scintigraphic defect from early images to follow-up examination was required before the defect was labeled as related to stress.

According to the method of Richie et al,[1] the anatomic location of the perfusion defect was determined from the left anterior oblique view in which the medial wedge represents the left anterior descending coronary distribution (an anterior defect); the posterolateral wedge, the circumflex coronary distribution (a posterior defect); and the inferior wedge, the posterior descending coronary distribution (an inferior defect). With the exception of the perfusion defects at the apex, image abnormalities were not considered defects unless they were visualized in the left anterior oblique view. Each set of early and follow-up scintigrams was read independently by 2 observers without knowledge of the clinical or cineangiographic data. The 2 independent observers agreed completely regarding the presence or absence of perfusion deficits in all but 8 instances. The disagreements in these 8 instances were resolved by adding a third observer and the final interpretation was then based on a consensus of 2 of 3 observers.

Thallium-201 scintigraphy with exercise: Within 1 week of cold pressor thallium-201 scintigraphy, 16 patients were exercised on a treadmill to a symptom-limited maximum. Heart rate and blood pressure were monitored continuously. Thallium-201 (1.5 to 2 mCi) was injected 1 minute before termination of the exercise. Scintigrams were obtained immediately after the exercise and 4 to 6 hours later. Analysis and interpretation of the scintigrams were carried out as described in the preceding section. Thallium-201 scintigrams during exercise could not be obtained in 13 patients, because 7 urgently required coronary bypass surgery and 6 others were unwilling to participate in an additional exercise test.

Thallium-201 scintigraphy at rest: To exclude the possibility that transient deficits of myocardial perfusion might have occurred independent of the stress intervention, we performed resting thallium-201 scintigraphy in 6 patients with triple vessel disease. All of these 6 patients had had transient perfusion deficits after the cold pressor and exercise tests. Thallium-201 scintigraphy was then performed at rest, without intervention, and repeated 4 hours later.

Coronary cineangiography during the cold pressor test: The mechanism of ischemia during the cold pressor test was examined in 6 patients and the possibility of coronary spasm as a cause was evaluated by performing coronary cineangiography before and during the cold pressor challenge. Coronary cineangiograms obtained before and during the cold pressor test were compared.

Results

A positive electrocardiographic exercise stress test was recorded in 18 of 24 patients with coronary artery disease and in 1 of 5 patients without coronary artery disease (a sensitivity of 75% and specificity of 80% for the whole group). Sensitivity was low (50%) in patients with single vessel disease. The patient with normal coronary angiograms and false-positive exercise stress test was not receiving digoxin or diuretics at the time of the test.

TABLE I Thallium-201 Scintigraphic and Exercise Electrocardiographic Data

	Total Patients (n)	Systolic Pressure × Heart Rate (Mean ± SD)		Patients (n) With Positive Changes/Total Patients				
		Baseline	Thallium-201 Injection*	1 Vessel CAD	2 Vessel CAD	3 Vessel CAD	No CAD	Sensitivity†
Cold pressor thallium-201 scintigraphy	36	77.4 ± 16	103.6 ± 17.0‡	4/10	10/11	10/10	0/5	77%
Exercise ECG	29	75.2 ± 11.7	210.8 ± 8.3‡	5/10	5/6	8/8	1/5	75%
Exercise thallium-201 scintigraphy	16	72.3 ± 8.2	202.6 ± 7.3‡	2/2	3/3	6/6	0/5	100%
Resting thallium-201 scintigraphy	6	77.6 ± 8.2	77.6 ± 8.2	. . .	. . .	1/6	. . .	. . .

* Injections were performed at 30 to 60 seconds of the cold pressor test during cold pressor scintigraphy, at peak exercise during exercise scintigraphy, and at rest during resting scintigraphy. † Sensitivity figures are for total patients. ‡ $p < 0.0005$ compared with baseline.
CAD = coronary artery disease; ECG = electrocardiogram.

The scintigraphic data are presented in Table I. After the cold pressor test, an increase in the systolic blood pressure × heart rate product (double product) was observed in all patients. The mean double product for the group was significantly higher at 30 seconds of the cold pressor test ($p < 0.0005$) (*t* test for paired data). After the initial increase in the double product at 30 seconds, no further significant increase occurred at 2 minutes of the cold pressor test. Both heart rate and blood pressure returned to baseline values within 5 minutes of the termination of the test in all patients. In addition to the changes in the double product, angina developed in 4 patients during the test and a >1 mm S-T segment depression in the electrocardiogram was observed in 3 of these 4 patients. In 5 patients, frequent unifocal premature ventricular contractions were observed during the test with complete resolution after the test. In none of the patients did sustained angina or new changes in the 12-lead electrocardiogram obtained 4 to 6 hours after the test develop.

Transient perfusion deficits were observed in 24 of 31 patients with coronary artery disease (a sensitivity of 77%). The sensitivity for the detection of coronary artery disease was high in patients with double and triple vessel disease (Table I). The location of a perfusion defect generally corresponded to that of a stenotic vessel in all patients with single vessel disease. Transient perfusion deficits, however, did not generally distinguish patients with single vessel disease from those with double and triple vessel disease. Only the most severely ischemic area among the several that may be present in patients with 2 and 3 vessel disease was identified. All 5 patients without coronary artery disease had normal scintigrams. Figure 1 shows representative scintigrams obtained early and late after the cold pressor test.

Thallium-201 scintigrams after symptom-limited maximal exercise stress test were obtained in 16 patients. Eleven patients (6 with triple, 3 with double, and 2 with single vessel disease) had positive scintigrams after exercise. All of these 11 patients also had positive scintigrams after the cold pressor test. The 5 patients with normal coronary cineangiograms had normal exercise scintigrams. The sensitivity level of cold pressor thallium-201 scintigraphy in detecting coronary artery disease was not significantly different from the sensitivity levels obtained during exercise scintigraphy and exercise electrocardiography (chi-square test for inde-

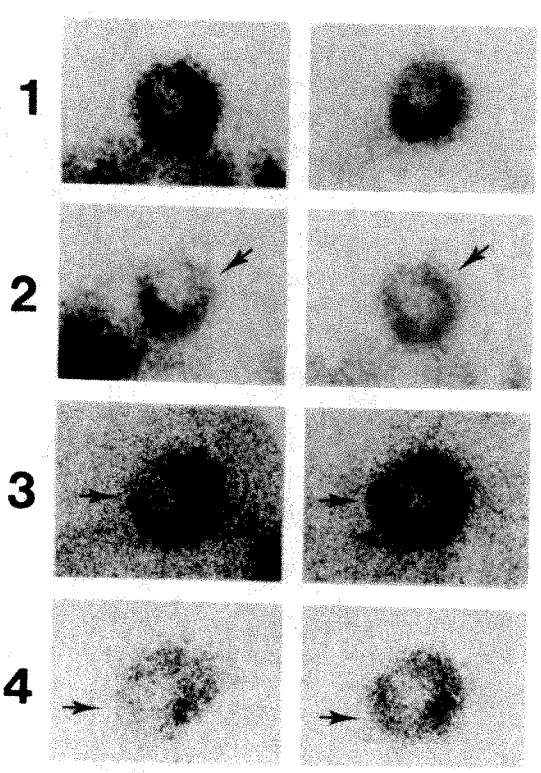

FIGURE 1. Thallium-201 scintigrams (45° left anterior oblique projection), immediately after the cold pressor test (**left**) and 4 hours later (**right**). Normal scintigrams in a patient with normal coronary angiograms (**panel 1**), abnormal scintigrams in patients with single vessel disease (circumflex vessel) (**panel 2**), double vessel disease (left anterior descending and right coronary vessels) (**panel 3**), and triple vessel disease (**panel 4**). **Arrows** point to the areas of transient perfusion deficits.

pendence). The site of the transient perfusion deficits observed in the 45° left anterior oblique cold pressor thallium-201 scintigrams was identical to the site of the perfusion deficits observed in the 45° left anterior oblique exercise thallium-201 scintigram in 8 patients. Anterior perfusion deficits were observed in 6 patients with triple vessel disease, in 1 patient with double vessel disease (left anterior descending and right coronary artery), and in 1 patient with single vessel disease (isolated left anterior descending lesion). Cold pressor scintigraphy induced posterior perfusion deficits in 2 patients with double vessel disease (right coronary and circumflex vessels) whereas with exercise scintigraphy the perfusion deficits appeared in the inferior region. In 1 patient with an isolated high grade (>90%) proximal lesion of a dominant circumflex coronary artery the perfusion deficit was high posterior during the cold pressor test and inferior during the exercise. Among the 6 patients who had thallium-201 scintigraphy performed at rest, only 1 patient showed a mild transient perfusion deficit in the early scintigram in the absence of angina or the electrocardiographic changes of ischemia. The perfusion deficit was smaller than the one observed in the cold pressor thallium-201 scintigram and resolved completely in the follow-up scintigram. No transient deficits of perfusion were observed in the remaining 5 patients. Permanent perfusion deficits were observed in 2 patients with a previous transmural myocardial infarction at rest as well as during the cold pressor scintigraphy. The 3 patients with a previous nontransmural myocardial infarction demonstrated no permanent perfusion abnormality.

The mean double product achieved at 30 seconds of the cold pressor test during coronary cineangiography in 6 patients with coronary artery disease was 101.3 ± 10.24 and was not significantly different from that attained during cold pressor thallium-201 scintigraphy (99.7 ± 9.3) (t test for paired data). Coronary spasm, either focal or generalized, was not detected in any of these 6 patients with positive cold pressor and exercise thallium-201 scintigrams.

Discussion

The cold pressor test is a simple and effective alpha-adrenergic stimulus.[2,3,6] Because a rapid increase in blood pressure and heart rate occurs during cold pressor stimulation, a number of recent investigations have focused on its use as a stress test in patients with coronary artery disease.[3,7,8] Wainwright et al[3] evaluated left ventricular function in normal subjects and in patients with coronary artery disease by performing radionuclide angiography during the cold pressor test. An increase in the left ventricular ejection fraction was reported in normal subjects. In patients with coronary artery disease, reduction in ejection fraction and development of regional wall motion abnormalities were observed. In other studies, increased coronary vascular resistance[7] and angiographic evidence of coronary artery spasm[9] were observed during the cold pressor test. The simple technique of cold pressor stimulation, its effectiveness in challenging the circulatory system, and its apparent innocuous nature led us to investigate its role in evaluating myocardial perfusion in patients with coronary artery disease.

Our preliminary results with cold pressor thallium-201 myocardial scintigraphy were encouraging. Transient perfusion deficits were observed in the thallium-201 scintigrams, after the cold pressor test, in 24 of 31 patients with coronary artery disease, and all 5 patients with normal coronary angiograms had normal scintigrams. As reported with exercise thallium-201 scintigraphy,[1] the detection of coronary artery disease with cold pressor thallium-201 scintigraphy was highest in patients with double and triple vessel disease. All patients with coronary artery disease, who had exercise-induced ischemic changes in the electrocardiograms and in the thallium-201 scintigrams, also had positive cold pressor thallium-201 scintigrams. In 5 patients without coronary artery disease, both cold pressor and exercise thallium-201 scintigraphy were equally specific in ruling out the presence of coronary artery disease.

Of 5 patients with previous myocardial infarction, only 2 patients with a discrete left ventricular aneurysm demonstrated permanent perfusion deficits in addition to the adjacent transient perfusion deficits in the cold pressor thallium-201 scintigram. Ten patients (5 patients with and 5 without previous myocardial infarction) demonstrated depressed left ventricular ejection fractions or regional wall motion abnormality, or both, at the time of cardiac catheterization. Abnormal left ventricular function in patients without evidence of previous myocardial infarction may be related to the development of ischemia at the time of left ventricular angiography or may be due to the presence of an unrecognized previous myocardial necrosis in some of these patients.

Gewirtz et al[10] reported that redistribution of thallium-201 in myocardial segments with initially low thallium-201 uptake may occur at rest, suggesting that transient perfusion abnormalities seen in some patients may be independent of stress intervention. The absence of transient perfusion deficits in the resting thallium-201 scintigrams in 5 of our patients with positive cold pressor thallium-201 scintigrams, however, suggests that scintigraphic changes in these patients were due to the cold pressor test. In 1 patient with triple vessel disease and a mild degree of resting redistribution, the transient perfusion abnormalities were more pronounced during the cold pressor test. The similarity or adjacent nature of the site of the perfusion abnormality in 10 of 11 patients with positive cold pressor and exercise thallium-201 scintigrams further validates the relation of the perfusion deficits to the stress intervention.

There are a few reports in the literature regarding the possible mechanisms involved in altered myocardial perfusion during the cold pressor challenge.[2,9,11] Feldman et al[9] recently reported an increase in coronary vascular resistance in the angiographically defined potentially abnormal regions (>50% coronary artery narrowing) during the cold pressor test. Their study concluded that the increase in coronary resistance was

not due to coronary spasm but possibly to a differential effect of an increased left ventricular end-diastolic pressure on regional blood flow. Thus, it appears that in patients with coronary artery disease, a heterogeneous myocardial perfusion is possible during the cold pressor test, with only modest increases in the double product and without any angiographic evidence of coronary spasm. Mudge et al,[7] however, did not observe increased left ventricular diastolic pressure in some of their patients with increased coronary vascular resistance during cold pressor stimulation. In their study,[7] a decrease in coronary blood flow and an increase in coronary vascular resistance were thought to be due to coronary vascular constriction secondary to alpha-adrenergic stimulation during the cold pressor test. In our study, the double products achieved during cold pressor stimulation were significantly lower than those obtained during exercise, which indicates that an increase in myocardial oxygen demand was probably not the primary mechanism responsible for perfusion abnormalities. The possibility that coronary spasm may have played a role in producing perfusion deficits cannot be excluded. No coronary spasm was detected, however, in 6 patients in whom coronary angiograms were obtained during the cold pressor test.

In summary, our data for the first time provide objective evidence of altered myocardial perfusion during cold pressor stimulation in patients with coronary artery disease. Cold pressor thallium-201 scintigraphy offers promise in detecting abnormal myocardial perfusion and appears to be sensitive in identifying patients with severe coronary artery disease. The limitations of standard exercise thallium-201 scintigraphy became obvious to us during the course of this study in that we were not able to exercise all of our patients. In comparison, the cold pressor challenge was performed with relative ease in all patients. Thus, the cold pressor test may find a diagnostic role in those patients in whom exercise stress test is not feasible. In our experience, cold pressor stimulation is safe and effective and can be performed easily at the patient's bedside. The exact physiologic mechanisms that become operational at the level of the coronary circulation during the cold exposure need further clarification. Our data indicate that further studies in a larger number of patients are warranted in order to define more clearly the sensitivity, specificity, and safety of cold pressor thallium-201 myocardial scintigraphy in patients with coronary artery disease.

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Plasma Beta-Thromboglobulin as a Measure of Platelet Activity

Effect of Risk Factors and Findings in Ischemic Heart Disease And After Acute Myocardial Infarction

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The plasma concentration of beta-thromboglobulin (BTG), a platelet-specific protein released during platelet aggregation, is considered a sensitive marker of in vivo platelet activity. The mean plasma level in 133 asymptomatic individuals was 32.3 ± 1.1 ng/ml, and there was no difference between those with no risk factors (32.2 ± 1.2 ng/ml, n = 56), those who smoked (31.8 ± 1.8 ng/ml, n = 45), those with hyperlipidemia (32.8 ± 1.7 ng/ml, n = 15), and those exposed to both of these risk factors (34.1 ± 2.7 ng/ml, n = 17). The mean plasma BTG level in 104 patients with symptomatic ischemic heart disease was significantly elevated (40.9 ± 1.4 ng/ml, p <0.01), but there was considerable overlap with normal levels. Although no difference was found between patients with no risk factors (38.1 ± 4.0 ng/ml, n = 13) and those with only 1 risk factor (37.0 ± 1.8 ng/ml, n = 44), patients with 2 or more risk factors had a significantly elevated plasma BTG level (45.2 ± 2.2 ng/ml, n = 47, p <0.01). It is concluded that risk factors themselves do not increase platelet activity, but that patients with vascular disease have activated platelets that may contribute to the progression of the disease. Plasma BTG was also measured serially for 10 days in 29 patients after hospitalization with acute ischemic cardiac pain. Although the median plasma level was elevated above normal there were no acute changes in plasma BTG after either acute infarction (n = 22) or acute ischemia (n = 7), except in 2 patients in whom pericardial friction rubs developed. Thus, measurement of systemic plasma BTG did not detect platelet involvement in acute coronary occlusion or acute ischemia.

Recent studies have highlighted the importance of coronary arterial thrombosis in both acute myocardial infarction and possibly unstable angina pectoris.[1–3] Occlusive arterial thrombosis results from a focus of platelet aggregation, and altered platelet behavior has been well documented in patients with ischemic heart disease.[4–6] However, it remains uncertain whether this alteration in platelet activity causes atherosclerosis and is exacerbated by the presence of known coronary risk factors, or whether it is due to the presence of established arterial disease activating the platelets secondarily.

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The plasma level of BTG, a platelet-specific protein released from platelet alpha granules during platelet aggregation, provides an accurate measure of in vivo platelet activity.[7] We report herein the results of measurements of plasma BTG in patients with symptomatic ischemic heart disease and in normal asymptomatic individuals and compare the effect of known coronary risk factors on platelet activity in the 2 groups. We also report the results of studies on changes in plasma BTG in patients after their admission to the Coronary Care Unit with chest pain to identify changes in platelet activity after acute myocardial infarction.

Methods

We studied 104 patients (76 male and 28 female) ranging in age from 27 to 65 years (mean age 51 years). All had a history of current exercise-induced angina pectoris and a resting or exercise electrocardiogram compatible with the diagnosis of ischemic heart disease. Patients with any recent change in

symptoms and those with an elevated creatinine level or additional valve disease, which might affect the plasma BTG level, were excluded. Fifty-five had previously documented myocardial infarction. Sixty-three patients were on beta-blocking drugs and 30 of these were on additional long-acting nitrates or calcium antagonist drugs. Twenty had undergone coronary arteriography and all demonstrated occlusive coronary atherosclerosis.

The smoking habits, blood lipid levels, blood pressure, and family history of ischemic heart disease were documented for each patient. A family history was considered positive for any patient who had a first-degree relative presenting with clinical ischemic heart disease under the age of 60 years. A smoker was defined as a patient who was still smoking at least 10 cigarettes a day. Hyperlipidemia was diagnosed when the serum cholesterol level was >7.0 mmol/liter or the serum triglyceride level was >1.8 mmol/liter in a strict fasting blood specimen despite treatment with diet, drugs, or both. A diastolic pressure >90 mm Hg despite antihypertensive treatment on at least 2 occasions was taken to indicate significant hypertension. No patient had taken aspirin or other anti-inflammatory drugs during the 10 days before sampling.

Blood was taken to determine plasma BTG, platelet count, and serum cholesterol and triglyceride levels during fasting. To prevent ex vivo platelet release and spurious elevation of plasma BTG, all blood samples were carefully collected by 1 of us (CWP), placed in prechilled platelet inhibitor solution, and processed within 1 hour.[7] Samples were assayed for BTG using the double-antibody technique described by Bolton et al,[8] which has an interassay coefficient of variation of 8%.

The results were compared with those of a control group of 101 blood donors (52 male and 49 female subjects) ranging in age from 18 to 64 years (mean 39) who had no history of vascular disease, renal disease, or hypertension and no family history of premature coronary disease. Blood lipid levels were checked at the time of sampling and only those with normal values were included. Their smoking habits were documented. An additional 32 subjects (22 male and 10 female) ranging in age from 22 to 63 years (mean 41) who had no clinical vascular disease but who were attending the Lipid Clinic because of hyperlipidemia were also examined.

In a separate study the platelet activity was measured in 30 patients admitted to the Coronary Care Unit with a diagnosis of possible acute myocardial infarction. Blood for BTG and platelet count was taken usually within 12 hours of the onset of symptoms (minimum 3 hours, maximum 20 hours) and then daily for 10 days or until the patient was discharged. Myocardial infarction was diagnosed on the basis of the conventional criteria of electrocardiographic changes and elevation in cardiac enzyme levels. Medical complications, particularly clinical evidence of deep venous thrombosis, elevated plasma creatinine levels, additional chest pain, pericarditis, or heart failure, were documented. The patients' records were then reviewed at 8 months after discharge from the hospital.

Results in asymptomatic individuals and patients with stable ischemic heart disease are expressed as mean ± standard error. Statistical analysis was carried out using the unpaired Student's t test. Results in patients followed up serially are expressed as a median value, and analysis was carried out using the Wilcoxon rank sum test.

Results

Plasma BTG in clinically asymptomatic subjects: Mean plasma BTG concentrations in relation to the presence of identified risk factors for normal asymptomatic subjects are shown in Figure 1. There was no significant difference between smokers (31.8 ± 1.6 ng/ml, n = 45) and nonsmokers (32.2 ± 1.2 ng/ml, n = 56). Hyperlipidemic subjects with no clinical evidence of vascular disease had normal BTG levels (32.8 ± 1.7 ng/ml, n = 15) and an additional 17 of these individuals who also smoked had a similar mean BTG level (34.1 ± 2.7 ng/ml). No correlation was found between serum cholesterol or triglycerides and plasma BTG in hyperlipidemic subjects, nor was there a difference in BTG concentration among the different classes of hyperlipidemia.

Plasma BTG in patients with stable symptomatic ischemic heart disease: Patients with coronary artery disease, however, had a significantly elevated mean

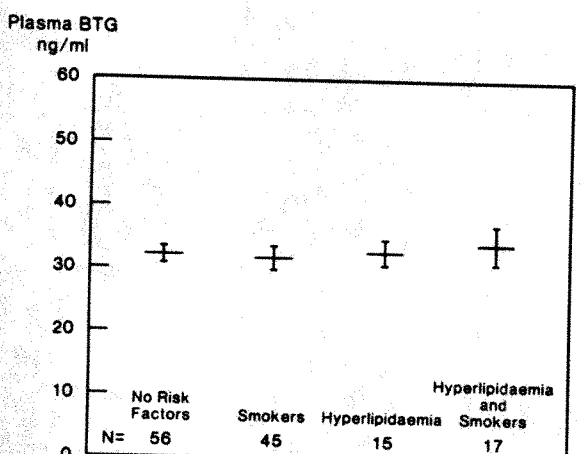

FIGURE 1. Plasma BTG in asymptomatic subjects: relation to risk factors.

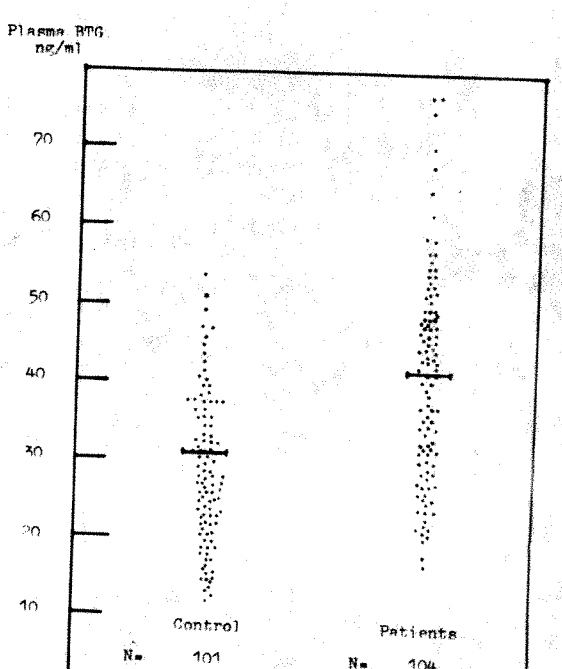

FIGURE 2. Mean and distribution of plasma BTG among control subjects and patients with ischemic heart disease.

plasma BTG level (40.9 ± 1.4 ng/ml, n = 104, p <0.01), although there was considerable overlap with the normal range (Fig. 2). A history of previous myocardial infarction or treatment with beta-blocking drugs or calcium channel-blocking drugs did not affect plasma BTG.

The plasma BTG level was not higher in patients with ischemic heart disease who had a single risk factor compared with those with no identifiable risk factor (Fig. 3). Patients with only a positive family history as a risk factor had a higher mean plasma BTG level than did patients with other risk factors, but for such a small group it was not statistically significant. However, when 2 or more risk factors were present, the mean plasma BTG level was significantly higher (45.2 ± 2.2 ng/ml, n = 47) than that in patients with 1 or no risk factors (37.3 ± 1.6 ng/ml, n = 57, p <0.01) (Fig. 4). No difference was observed between patients with 2 and the small number with 3 (n = 12) or 4 (n = 2) risk factors.

Plasma BTG level after acute chest pain: Of the 30 patients admitted with chest pain, 22 had transmural myocardial infarcts. Seven subsequently had no evidence of infarction and were considered to have unstable angina. One patient was thought to have esophageal pain and was subsequently shown to have normal coronary arteries. Plasma BTG concentrations both in patients with infarct and in those with angina were higher than normal through the period studied, but there was no overall change in median plasma BTG levels with time in either group and no difference between the 2 groups (Fig. 5). The patient with esophageal pain had normal BTG values.

In 2 patients a pericardial friction rub developed which was associated with an acute temporary increase in BTG level, in 1 patient to 74.5 ng/ml and in the other to 95.1 ng/ml. Four patients had additional cardiac pain, with no evidence of infarction extension and no significant alteration in plasma BTG level. In 5 patients heart failure developed with, again, no change in BTG level. In no patient did clinical signs of venous thrombosis, arterial embolism, or an increase in plasma creatinine level develop.

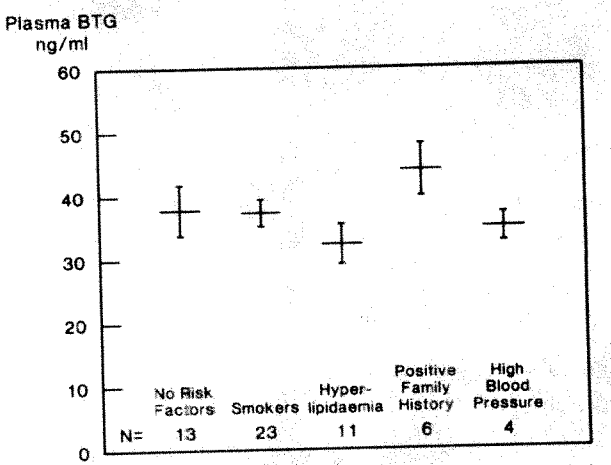

FIGURE 3. Plasma BTG in patients with ischemic heart disease: relation to risk factors.

After 8 months, 2 of the 29 patients had died suddenly (median BTG level on hospital discharge 34.0 ng/ml). One had had another infarct (BTG 37.4 ng/ml) and 8 continued to have angina pectoris (median BTG level 37.9 ng/ml). The other 18 patients were alive with no symptoms (median BTG level 45.1 ng/ml).

Discussion

These results support the concept that platelets function abnormally in patients with ischemic heart disease, evidence for which includes both increased in vitro platelet aggregation and accelerated in vivo platelet consumption.[4-6,9,10] Although the mean age of the control subjects was lower than that of the study group, age is not an independent determinant of plasma BTG levels.[7] The increased platelet activity in our patients was not detectably augmented by single risk

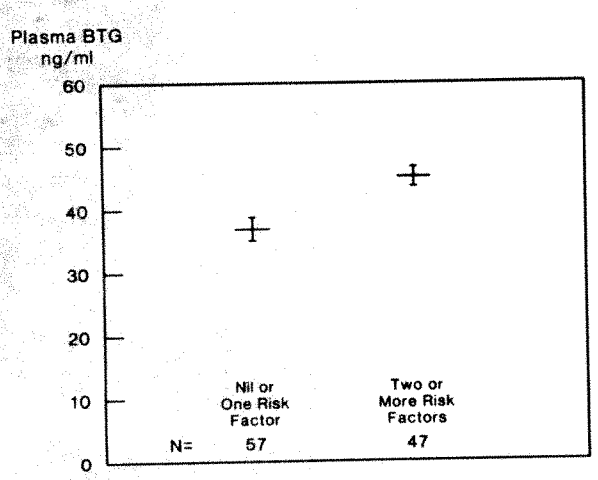

FIGURE 4. Plasma BTG in patients with ischemic heart disease. Comparison of those with 1 or no risk factors to those with 2 or more risk factors.

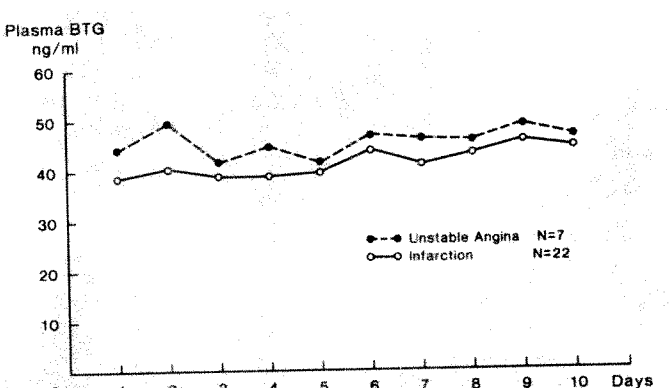

FIGURE 5. Changes in plasma BTG after admission with chest pain (median values).

factors, although in patients with 2 or more risk factors the plasma BTG level was significantly increased. Such risk factors may operate synergistically, and each may have an effect that is not detectable unless these effects are combined. Alternatively, vascular disease may activate platelets which then contribute to further progression of the atherosclerotic process. The increased platelet activation seen in hypertension has been attributed to the existence of established atherosclerosis caused by hypertension rather than to a direct effect on the platelets.[11] Although not all patients who present with cardiac pain have fixed coronary artery stenosis, it was found in the 20 patients who underwent coronary arteriography. Therefore, the higher plasma BTG levels found in our patients with more risk factors may indicate more extensive disease throughout the arterial system.

Our data on normal asymptomatic individuals with the identified coronary risk factors of smoking and hyperlipidemia reinforce this finding. Thus, although our definition of a risk factor was arbitrary, we did not find that the presence of risk factors per se in otherwise healthy subjects significantly affected platelet activity. Although others[12,13] showed altered platelet activity in various types of hyperlipidemia, we found normal plasma BTG levels in asymptomatic patients with hyperlipidemia. In addition, although reduced platelet survival has been reported in apparently healthy smokers,[14] our control subjects who smoked had normal plasma BTG levels and, furthermore, the 17 asymptomatic subjects with both risk factors had no exacerbation of platelet activity. It is likely that platelet survival and plasma BTG do not reflect similar aspects of platelet activity.

Our failure to demonstrate a change in plasma BTG levels after infarction is surprising in view of recent evidence that coronary thrombosis occurs early in the evolution of infarction and may even initiate it.[1,2] Although we were unable to measure plasma BTG levels before infarction, samples were taken as early as 3 hours after the event. If considerable BTG release had been associated with infarction, a subsequent decline in plasma BTG levels from an initial high level should have been observed. Our negative findings suggest that either BTG, with its short half-life, was cleared from the blood before the samples were taken or that the amount of BTG released from a platelet thrombus occluding a coronary artery is not sufficient to cause a measurable increase in the systemic circulation. Furthermore, our findings differ from those of Smitherman et al,[15] who found in some cases very high levels of plasma BTG, although the temporal relation between peak plasma level and infarction was inexact. No reference is made to factors other than ischemia, such as pericarditis, altered renal function, venous thrombosis, or intercurrent infection, which might have contributed to these elevated plasma values.

Similarly, in contrast to another report,[16] we found no increase in plasma BTG levels after episodes of unstable angina. In the few patients who had continuing symptoms after admission, blood samples were taken very shortly after the symptoms were relieved and still no alteration in plasma BTG was observed. Platelet thrombosis is probably not involved in the pathogenesis of unstable angina; alternatively, as already mentioned, systemic venous sampling is not sensitive enough to detect BTG released from platelets in the coronary circulation.

The months after infarction are the period of increased risk of death or reinfarction. We found no correlation between plasma BTG and clinical history during the 8 months after discharge from the hospital. Plasma BTG did not distinguish the 2 patients who died suddenly or those who continued to have angina pectoris, so there is no suggestion that plasma BTG will identify patients with a poor prognosis.

We conclude that elevated plasma BTG levels in patients with ischemic heart disease probably reflect platelet activation by established vascular disease. However, measurement of plasma BTG unable to detect platelet involvement in myocardial infarction or unstable angina pectoris.

Acknowledgment: We are grateful to Professor M. Oliver and the staff of the Cardiac Department of the Royal Infirmary, Edinburgh, Scotland, for permission to study their patients.

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Use of QRS Scoring and Thallium-201 Scintigraphy to Assess Left Ventricular Function After Myocardial Infarction

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To determine the usefulness of the QRS scoring system in predicting left ventricular function, and the correlation between the QRS score, left ventricular ejection fraction, and the size of infarction, patients with acute or chronic infarction were studied by means of 12-lead electrocardiography, rest thallium-201 scintigraphy, and radionuclide angiography.

In patients with acute infarction there was a statistically significant correlation between the QRS score and the left ventricular ejection fraction ($n = 28$, $r = -0.61$, $p < 0.001$), between the thallium score (as a measure of the extent of necrosis) and the left ventricular ejection fraction ($n = 21$, $r = 0.70$, $p < 0.001$), and between the QRS score and the thallium score ($n = 22$, $r = -0.65$, $p < 0.001$). A QRS score of 2 or less separated patients with left ventricular ejection fraction of 40% or greater from those with lower left ventricular ejection fraction ($p < 0.01$).

In patients with chronic infarction there was a wide scatter of ejection fraction for any given QRS score ($n = 41$, $r = -0.51$). In a subset of patients with chronic infarction before they underwent coronary artery bypass, there was still a fair correlation between thallium score and left ventricular ejection fraction ($n = 15$, $r = 0.61$, $p < 0.02$) but not between thallium score and QRS score ($r = 0.03$, $p > 0.05$). In addition, in these patients with chronic infarction who underwent coronary revascularization, there was still a fair correlation between the postoperative thallium score and the postoperative left ventricular ejection fraction ($r = 0.75$, $p < 0.05$) but not between the postoperative thallium score and the postoperative QRS score ($r = 0.02$, $p > 0.05$) or between the QRS score and the ejection fraction ($r = 0.24$, $p > 0.05$).

The size of the defect appears related to the left ventricular ejection fraction in both patients with acute infarction and those with chronic infarction. The QRS scoring system in patients with acute infarction and the size of the thallium defect in patients with acute or chronic infarction can categorize patients into those who have a low, moderate, and normal ejection fraction.

Left ventricular performance is an important factor in determining prognosis in patients with chronic coronary heart disease as well as after acute myocardial infarction.[1–5] Techniques that have been used as prognostic indicators after acute infarction include evaluation of left ventricular ejection fraction and wall motion by radionuclide angiography[6] and evaluation of the size of the scarred or ischemic myocardium by rest thallium-201 scintigraphy.[7] In addition, a specific appearance of the technetium-99m pyrophosphate images has been correlated with poor prognosis.[8] Finally, exercise testing with or without thallium-201 imaging or radionuclide ventriculography has been used to categorize patients after acute infarction in different risk groups.[9,10]

Recently, Palmeri et al,[11] using a QRS scoring system, were able to evaluate left ventricular function in patients with acute myocardial infarction. The QRS scoring system was still fairly accurate in predicting ventricular function up to 1 year after acute infarction in the group of patients they followed up.

We were intrigued by the fact that a QRS score would work at all. If it does, then it is probably due to electrical

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forces from viable myocardium. The other noninvasive way to demonstrate viable myocardium is thallium-201 imaging. Furthermore, if there is a change in left ventricular ejection fraction as a result of improvement in myocardial flow by coronary artery bypass surgery, a change of QRS score might be expected as well and probably an improvement in the thallium perfusion defect.

The purpose of this study was to compare the usefulness of the QRS scoring system of 12-lead electrocardiograms with that of resting thallium-201 scintigrams in evaluating the left ventricular function of patients with acute or old myocardial infarction before and after coronary artery bypass.

Methods

We studied 2 groups of patients. The first group consisted of 37 patients with the diagnosis of acute infarction confirmed by typical history, electrocardiographic changes, and elevation in serum enzyme and specific cardiac isoenzyme levels. These patients were admitted to the coronary care unit over a 2-month period. Thallium-201 images at rest are obtained in most patients with acute infarction admitted to our coronary care unit. The second group consisted of 43 patients with a documented history of myocardial infarction (more than 3 months before hospitalization) as determined by history, electrocardiography, and cardiac enzyme levels. Sixteen of the 43 patients subsequently underwent coronary bypass because of angina pectoris.

Standard 12-lead surface electrocardiograms were obtained with a 3-channel Hewlett-Packard recorder at a paper speed of 25 mm/s daily for 3 days and as clinically indicated afterward in 37 patients with acute myocardial infarction. If left ventricular hypertrophy, left anterior hemiblock (QRS axis $\geq -60°$), right or left bundle branch block, ventricular preexcitation, or nonspecific intraventricular delay (QRS ≥ 110 ms) was present on the electrocardiogram at 2 weeks, the patient was withdrawn from the study because the QRS score does not work in these patients. Using these exclusion criteria, we withdrew 8 patients from the study; therefore, 29 patients comprised the study group. Follow-up electrocardiograms were obtained at 2 weeks and compared with radionuclide angiograms performed at that time. Thallium-201 scintigraphy was performed at rest in 22 of the 29 patients 2 weeks after infarction as well. In the remaining 7 patients, thallium images were not obtained because either the patient or the treating physician refused the studies.

A transmural infarct was considered anterior or inferior when new Q waves ≥ 30 ms were present in the precordial leads or lead aVF, respectively. A non-Q-wave infarct was diagnosed when patients had a typical history of infarction with appropriate enzyme elevation, but in whom a Q wave ≥ 30 ms did not develop in the electrocardiogram.

The QRS scoring system was based on the system developed by Selvester et al.[12,13] Q- and R-wave durations and R/Q and R/S amplitudes and ratios in 10 of 12 standard electrocardiographic leads were analyzed (Table I). QRS scores could range from a minimal value of 0 to a theoretical maximum of 29 points.

In patients with chronic infarction, radionuclide angiograms were not available soon after acute infarction. Each patient, however, subsequently underwent electrocardiography and radionuclide angiography. These patients were consecutive patients being evaluated in the nuclear cardiology laboratories for symptoms of angina pectoris. Sixteen of the 43 patients

TABLE I Criteria for Determining Point Score in the QRS Scoring System

Lead	Criteria (Number of Points)		Maximal Points
	Duration	Amplitude Ratio	
I	Q $\geq$30 ms (1)	R/Q $\leq$1 (1)	2
II	Q $\geq$40 ms (2) Q $\geq$30 ms (1)		2
aVL	Q $\geq$30 ms (1)	R/Q $\leq$1 (1)	2
aVF	Q $\geq$50 ms (3) Q $\geq$40 ms (2)	R/Q $\leq$1 (2)	5
V_1	Q $\geq$30 ms (1) Any Q (1) R $\geq$50 ms (2) R $\geq$40 ms (1)	R/Q $\leq$2 (1) R/S $\geq$1 (1)	4
V_2	Any Q or R $\leq$20 ms (1) R $\geq$60 ms (2) R $\geq$50 ms (1)	 R/S $\geq$1.5 (1)	4
V_3	Any Q or R $\leq$30 ms (1)		1
V_4	Q $\geq$20 ms (1)	R/Q or R/S $\leq$0.5 (2) R/Q or R/S $\leq$1 (1)	3
V_5	Q $\geq$30 ms (1)	R/Q or R/S $\leq$1 (2) R/Q or R/S $\leq$2 (1)	3
V_6	Q $\geq$30 ms (1)	R/Q or R/S $\leq$1 (2) R/Q or R/S $\leq$3 (1)	3

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subsequently underwent coronary artery bypass surgery. In 15 of the 16 patients, thallium-201 images at rest were also available preoperatively. Ten to 14 days after surgery, electrocardiography, thallium-201 imaging at rest, and radionuclide angiography at rest were repeated in all but 1 of these 15 patients.

Radionuclide angiography at rest was performed by means of a first-pass technique with a computerized multicrystal gamma camera (Baird-Atomic Systems-77) equipped with a 1-inch (2.54 cm) parallel-hole collimator positioned anterior to the precordium. The study was inadequate in 1 patient because of a poor bolus injection. The technique for measuring the ejection fraction has been described in detail from this[14] and other laboratories.[15]

In a previous study we showed an excellent correlation between radionuclide-derived ejection fractions and similar measurements obtained during cardiac catheterization.[14] The technique for thallium imaging was previously described in reports from this laboratory.[16–20] Quantitative analysis of the thallium images was performed by the perimetric method, as previously described from this laboratory.[18,19] The size of the thallium-201 defect was determined by measuring the perimeter with a computerized Hewlett-Packard 982A digitizer and expressing it as a percentage of the total left ventricular perimeter in each projection (Fig. 1). The region of the valve was excluded. This method is similar to that used by Field et al[3] in assessing the extent of akinetic-dyskinetic segments by means of left ventriculography. The percentage of the average abnormal perimeter was determined from 3 projections.

We also assessed the thallium scans by a scoring system. The image in each of the 3 projections was divided into 3 segments. Each segment was subjectively scored as follows: a score of 0 indicated minimal or no uptake; a score of 1 indicated severe reduction in uptake; a score of 2 indicated a moderate (but definite) reduction in uptake; a score of 3 indicated a mild (thus equivocal) reduction in uptake; and, finally, a score of 4 indicated normal uptake. Because the apex of the left ventricle usually has less thallium uptake than the remaining segments, presumably because the apex is thinner than the rest of the myocardium, we multiplied the score in

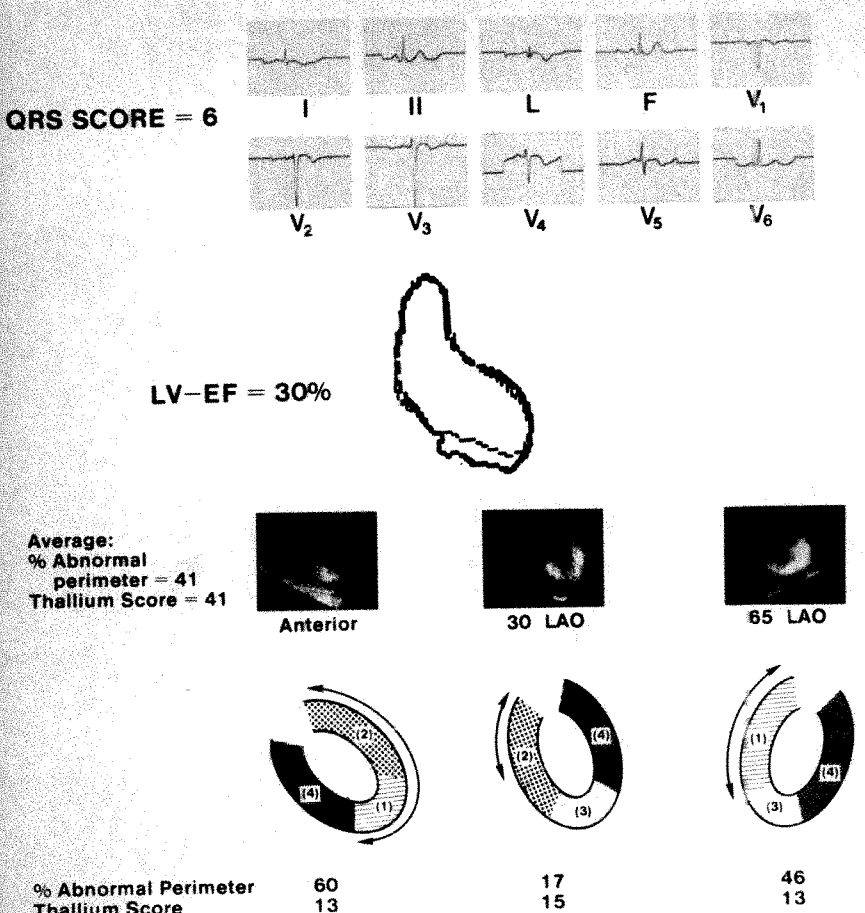

FIGURE 1. The QRS score, left ventricular (LV) radionuclide angiogram, and the thallium-201 images from a patient with acute anterior infarction. EF = ejection fraction; LAO = left anterior oblique projection.

the remaining segments by 2, yielding a score of 20 in each projection for a total score of 60 in 3 projections (Fig. 1). However, the results were not different even when a score of 4 was used for each segment. Therefore, a score of 40 would indicate that only two thirds of the left ventricle has normal uptake. Interpretations of the electrocardiogram, radionuclide angiograms, and thallium images were made independently without knowledge of the other results.

The inter- and intraobserver variability in measuring the left ventricular ejection fraction was 2.2 ± 1.5%[14] and the interobserver variability in measuring the thallium defects was 4 ± 4%; the maximal difference was 14% in a patient with large defects whereas the intraobserver variability in measuring the thallium defects was 3 ± 3%.[18,19] The intraobserver variability in measuring the QRS score was 2 ± 2% with a maximal difference of 5%.

Statistical analysis was performed using Student's *t* test or analysis of variance when appropriate. Values were expressed as the mean ± standard deviation (SD) when indicated. A probability (p) value less than 0.05 was considered to represent a statistically significant difference. Correlation between the variables was assessed with linear regression analysis.

Acute myocardial infarction: Of the 29 patients with acute infarction, the infarction was transmural (Q-wave infarction) in 20 patients: anterior in 9, inferior in 6, and both anterior and inferior in 5. The remaining 9 patients had non–Q-wave infarctions (nontransmural or subendocardial). There were 23 men and 6 women with an age range of 36 to 86 years (mean 61.2).

QRS scoring: Seven of the 29 patients (24%) had a QRS score of 2 or less. All 7 patients had non–Q-wave infarctions. In the remaining patients the QRS score varied between 3 and 18. Patients with transmural infarctions had higher scores than patients with non–Q-wave infarctions (8.3 ± 3.8 versus 1.6 ± 1.2, $p < 0.001$).

Left ventricular ejection fraction: The ejection fraction was ≥40% in 10 patients and <40% in the remaining 18 patients. The ejection fraction was significantly different in patients with transmural infarction and in patients with non–Q-wave infarction (28.7 ± 12.7% versus 45 ± 9.8%, $p < 0.001$).

Myocardial thallium-201 scintigraphy: Resting myocardial thallium-201 scintigrams were obtained 10 to 14 days after acute infarction in 22 patients. Twenty of the 22 patients (91%) had abnormal scans. There was a good correlation between the 2 methods used in this study in assessing perfusion defects, that is, perimetry versus scoring ($r = 0.91$, $y = 129.7 - 2.18x$) ($p < 0.001$) (Fig. 2). However, both sets of data (score and perimeter) were derived from the same image data and therefore such agreement is not unexpected. Validation of any method should be made by comparison with an independent, different method such as postmortem size of the infarction. However, such data were not available to us because none of the patients died during the study period.

Correlation between QRS score and left ventricular ejection fraction: There was an inverse correlation between ejection fraction and QRS score in the 28 patients with acute infarction in whom both studies were available ($r = -0.61$, y

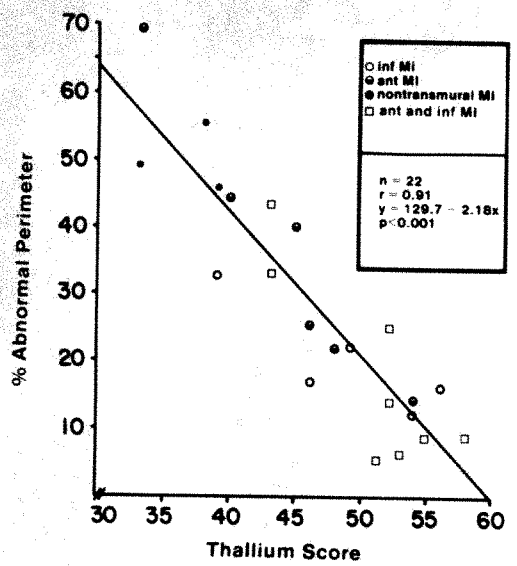

FIGURE 2. Comparison between thallium score and thallium percentage (abnormal perimeter) in 22 patients with acute myocardial infarction (MI). Ant = anterior; inf = inferior.

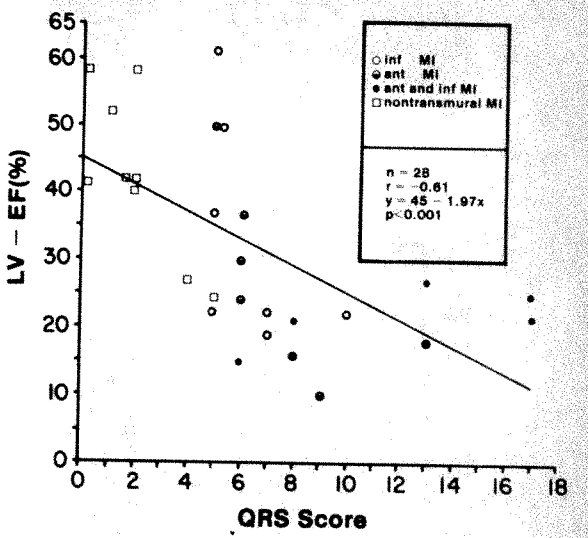

FIGURE 3. Comparison between QRS score and left ventricular ejection fraction (LV-EF) in 28 patients with acute infarction. Abbreviations as in Figure 2.

= 45 − 1.97x, p <0.001) (Fig. 3). All 7 patients with a QRS score ≤2 had an ejection fraction ≥40%. However, only 3 of the remaining 21 patients (14%) with a QRS score >2 had an ejection fraction ≥40% (p <0.01). In general, the higher the score, the lower the ejection fraction. Patients with a QRS score ≥10 had an ejection fraction of 30% or less.

Correlation between thallium-201 scintigrams and left ventricular function: As mentioned earlier, there was good agreement between the perimetric and scoring systems for evaluation of thallium scintigrams. We found a fair correlation between the size of the defect and the left ventricular ejection fraction (r = −0.71, y = 51.3 − 0.57x, p <0.001 by perimetry; and r = 0.70, y = 1.34x − 27.4, p <0.001 by thallium score)

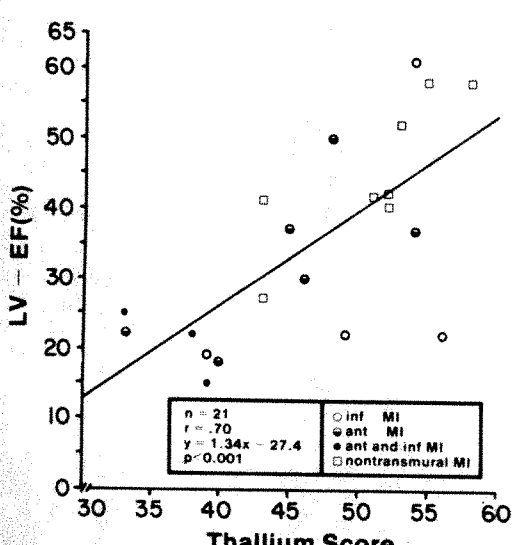

FIGURE 4. Comparison between the thallium score and left ventricular ejection fraction (LV-EF) in 21 patients with acute myocardial infarction. Abbreviations as in Figure 2.

(Fig. 4). Patients with small defects had higher ejection fractions than patients with larger defects. All 6 patients with a thallium score ≤40 had an ejection fraction ≤25%, whereas only 2 of 15 patients (13%) with a thallium score >40% had an ejection fraction <25% (p <0.01). Few exceptions were noted: 1 patient with a thallium score of 56 had an ejection fraction of 22%, and another patient with a score of 49 had an ejection fraction of 22%. The QRS score of the first patient was 5, also inappropriate for the level of ejection fraction, whereas the QRS score of the second patient was 10, appropriate for the corresponding ejection fraction of 22%. Apart from these exceptions, the higher the thallium score, the higher the ejection fraction in these patients.

Correlation between thallium score and QRS score: The correlation between the QRS score and the thallium score in patients with acute infarction (Fig. 5) was good (r = −0.65, y = 25.3 − 0.42x, p <0.001).

Patients with chronic myocardial infarction: Fifteen of the 43 patients had chronic anterior transmural infarction, 15 had chronic inferior transmural infarction, 2 had both anterior and inferior infarction, and 9 had non–Q-wave infarction. Two patients had bundle branch block and were excluded from QRS scoring. There were 37 men and 6 women, aged 35 to 69 years (mean 50.1). The left ventricular ejection fraction was measured in all 43 patients by first-pass radionuclide angiography. Although there was a statistically significant correlation between the QRS score and the left ventricular ejection fraction (Fig. 6), a wide scatter of ejection fractions was noted for a given QRS score. For example, for a score of 3, the ejection fraction ranged between 31 and 70%. The scatter was noted even at high QRS scores. Although 7 of 9 patients (77%) with a QRS score of 2 or less had a left ventricular ejection fraction >40%, 15 of 32 patients (47%) with a QRS score >2 also had an ejection fraction >40% (p not significant).

As indicated, 16 of these patients subsequently underwent coronary artery bypass. Resting thallium-201 scintigrams were available in 15 of the 16 patients preoperatively. Furthermore, 14 of these 15 patients had resting thallium scans 10 to 14 days postoperatively as well. The group of patients that underwent

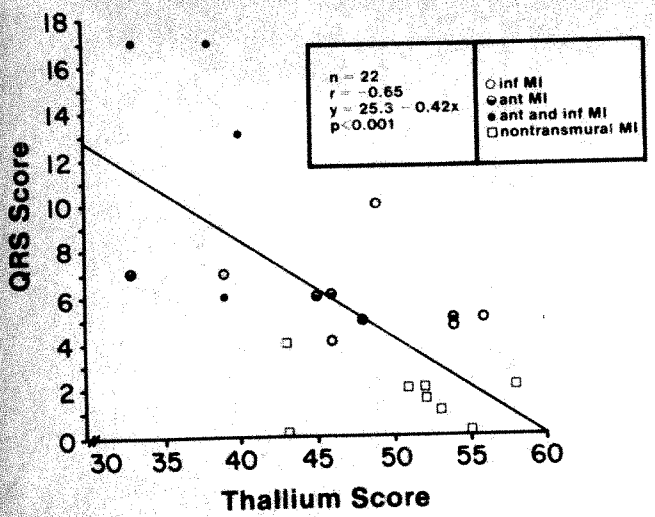

FIGURE 5. Comparison between QRS score and thallium score in 22 patients with acute myocardial infarction. Abbreviations as in Figure 2.

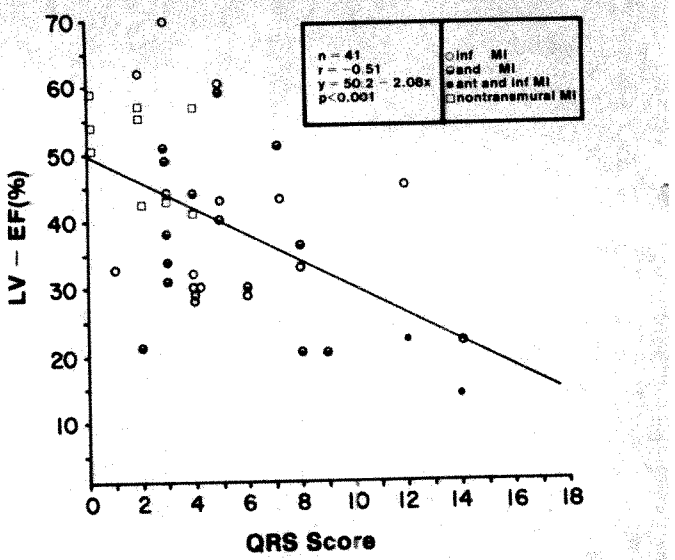

FIGURE 6. Comparison between QRS score and left ventricular ejection fraction (LV-EF) in 41 patients with chronic myocardial infarction. Abbreviations as in Figure 2.

surgery consisted of 14 men and 2 women, aged 41 to 69 years. Eight of the 16 patients had transmural inferior infarctions, 3 had transmural anterior infarctions, 1 had both anterior and inferior infarction, 2 had non–Q-wave infarction, and 2 had bundle branch block. The ejection fraction measured in 15 patients increased from 34 ± 8% preoperatively to 38 ± 12% postoperatively ($0.05 < p < 0.10$) and in the 14 patients who had both pre- and postoperative resting thallium scans, the thallium score improved from 40.7 ± 8.5 to 45.9 ± 9.0 ($p < 0.05$).

There was a fair correlation between the thallium score and the ejection fraction preoperatively in the 15 patients ($r = 0.61$, $y = 12.0 + 0.52x$) ($p < 0.02$) as well as between the postoperative ejection fraction and the postoperative thallium score in the 14 patients ($r = 0.75$, $y = -6.6 + 0.98x$, $p < 0.01$) (Fig. 7). The correlation between QRS score and ejection fraction was poor both pre- and postoperatively (p not significant). Similarly, there was a poor correlation between the QRS score and the thallium score both pre- and postoperatively (p not significant). Therefore, in these patients the QRS score had limited value in predicting left ventricular ejection fraction.

Discussion

The results of this study show that in patients with acute infarction, the QRS scoring system of Wagner et al[13] is reliable in predicting left ventricular function. Our study, therefore, confirms the conclusion of Palmeri et al,[11] although our correlation was lower than that reported by these investigators ($r = -0.61$ versus -0.88). It is worth emphasizing that the QRS scoring system cannot be used in patients with conduction defects, but can be used whether the myocardial infarction is transmural or nontransmural (non–Q-wave infarction). Although we studied a small group of patients with acute infarction, nevertheless these patients had a wide range of left ventricular function, QRS scores, and thallium scores and therefore these observations are likely to represent findings occurring more generally in other patients with acute infarction. Although a trend was observed in the correlation between the ejection fraction and the QRS score in patients with chronic myocardial infarction, the correlation was marginal ($r = -0.51$).

More important, careful analysis of Figures 3 and 6 shows that for any given score the ejection fraction varied widely in patients with chronic infarction but not in patients with acute infarction. These results are similar in some respects to those of Palmeri et al[11] but also show some differences. First, these investigators followed the same cohort of patients with acute infarction over 2 years. However, we studied entirely different groups of patients, 1 with acute infarction and 1 with

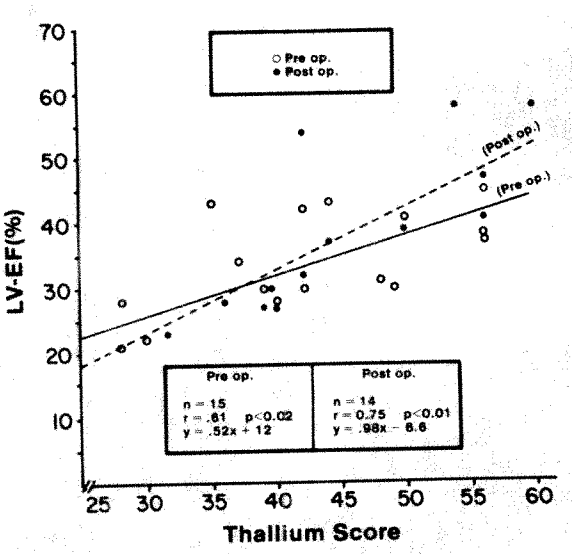

FIGURE 7. Comparison between thallium score and left ventricular ejection fraction (LV-EF) before and after coronary artery bypass surgery. Postop. = postoperative; precp. = preoperative.

chronic infarction. This difference in method is related to the design of the study—prospective in the case of Palmeri et al[11] and retrospective in our study. Second, even in the study of Palmeri et al,[11] the correlation between the QRS score and the ejection fraction was lower at 1 year than the correlation 2 weeks after acute infarction.

The exact reasons for the poorer correlation in patients with chronic infarction in both studies are not exactly known, but certain mechanisms can be postulated: for example, the disappearance of Q waves, a compensatory increase in the end-diastolic volume, and the effects of medications that may alter preload, afterload, and contractility. Finally, the presence or absence of myocardial ischemia at rest cannot be discounted.

It appears that the common denominator between the QRS score and the left ventricular ejection fraction is the amount of infarcted myocardium. A significant correlation between the extent of myocardial fibrosis and left ventricular function has been shown.[21] The extent of thallium defect has been shown to correlate with pathologically determined infarct size and with the contrast angiographic extent of asynergy.[22,23] We studied the extent of the infarcted myocardium in patients with acute infarction by means of thallium-201 scintigraphy at rest, and in fact found a fair correlation between the size of the perfusion defect, the ejection fraction, and the QRS score (Fig. 3 and 4). We also found that in patients with chronic infarction, the correlation between the size of the defect and the ejection fraction was still fair, but again we found a poor correlation between the QRS score and the size of the thallium defect in patients with chronic infarction.

In addition to fibrosis, resting thallium defects may represent chronic ischemia (or hypoperfusion). These perfusion abnormalities may be responsible for the segmental left ventricular wall-motion abnormalities seen in patients with chronic coronary artery disease in the absence of infarction: they may also explain the reversibility of these wall-motion abnormalities with nitroglycerin.[24] This assumption needs further study.

In the subgroup of patients with chronic infarction who underwent revascularization, the postoperative correlation between the ejection fraction and the size of the thallium defect was still fair (Fig. 7). However, as in the preoperative study, the correlation between the QRS score and the thallium score, or between the QRS score and the ejection fraction was poor. These results suggest that factors inherent in the QRS scoring system may be responsible for the poor correlation between the ejection fraction and the QRS score in patients with chronic infarction.

Our method for assessing the defect size seen on thallium scans is simple and may be performed in any laboratory. Moreover, the good correlation between a thallium scoring system and the perimetric method used in this study indicates that the scoring system may be preferred because of its simplicity. As noted earlier, the correlation between the 2 methods is not unexpected because both sets of data were derived from the same images. The ultimate validation of either method has to be made by a comparison with postmortem infarct size and probably with the contrast angiographic extent of asynergy as determined by other investigators.[22,23] However, neither postmortem nor contrast angiographic data were available in our patients. Even the defect size in the thallium scans did not correlate perfectly with the left ventricular ejection fraction ($r = 0.70$). There may be several related factors. First, some defects seen in the resting scans may represent ischemia (hypoperfusion) rather than scarring. Although it is our practice to obtain 4-hour delayed images after the initial resting images, the size of the defect as reported in this study represents the total defect size of both infarcted and possibly ischemic myocardium.

Second, the left ventricular ejection fraction may have been affected by factors that modify the preload, afterload, and contractility.[25] Third, as demonstrated in 2 patients with a small thallium defect in this study, the ejection fraction was disproportionately low compared with the size of the defect. In these patients an independent cardiomyopathic process may have been responsible for lowering the ejection fraction. It is well known that patients with nonischemic cardiomyopathy may have very low ejection fractions despite the presence of normal or near-normal left ventricular function[26] (Fig. 4 and 7).

Clinical implications: This study confirms a previous report that the QRS scoring system is of value in predicting left ventricular function in patients with acute infarction. With practice, the QRS score may be obtained in less than 1 minute. Therefore, this simple, inexpensive, and routinely available test is useful under these circumstances. However, caution should be applied in using the QRS scoring system in patients with old infarction. Although the QRS scoring system does not provide absolute measurements of the ejection fraction, it may help classify the patients into groups with normal or near-normal left ventricular function and mild to moderate left ventricular dysfunction. Furthermore, the size of infarction as assessed by thallium-201 correlated with left ventricular function in patients with acute or chronic infarction as well as in patients after revascularization surgery.

Finally, we should not be misled by a good p value, but should look rather at the spread of the data points. The ultimate purpose of these methods is to apply them clinically. It is clear that in individual patients, we cannot reliably predict left ventricular ejection fraction. The closest thing we can probably do is categorize the patients into those with low, moderate, and normal ejection fraction. This categorization could be done by using the QRS scoring system in acute infarction and by thallium imaging in patients with acute or chronic infarction.

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Current Incidence of Postmyocardial Infarction (Dressler's) Syndrome

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This study examines the current incidence of postmyocardial infarction (Dressler's) syndrome. During 1980, 282 patients with documented myocardial infarction were admitted to our coronary care unit. Early postmyocardial infarction pericarditis was present in 18 patients (6.4%). Six of these patients received steroids and the remainder were treated with salicylates or other anti-inflammatory drugs. Anticoagulation was used in 149 patients (53%) during hospitalization. One hundred forty-four (51%) were receiving heparin and 133 (47%) received no anticoagulation. Information on the patient's status at 6 months was available in 229 patients who were discharged alive. Sixteen patients had died within 6 months after discharge and 4 patients were lost to follow-up study. There were no documented cases of Dressler's syndrome.

It is concluded that Dressler's syndrome has decreased in incidence and perhaps disappeared. This decrease is most likely related to decreased use of oral anticoagulants and to more aggressive treatment of postmyocardial infarction pericarditis.

The postmyocardial infarction syndrome (Dressler's) was described at our medical center in 1956.[1] Clinical features of this syndrome include fever, chest pain, pericarditis, pleurisy, and pneumonitis and a tendency to recurrence.[2-4] Dressler[2] estimated that this complication occurred in 3 to 4% of recent myocardial infarctions. Our experience indicates that this syndrome has significantly decreased in frequency and perhaps no longer occurs. This study reports the current incidence of this complication and examines the possible explanations for this change.

Methods

The study population consisted of patients with a well-documented acute myocardial infarction who were admitted to our coronary care unit during 1980. The presence of acute myocardial infarction was established if the patient had electrocardiographic abnormalities consistent with the Minnesota code for acute myocardial infarction, in addition to typical symptoms of acute myocardial infarction and elevated serum enzyme levels. This electrocardiographic classification of acute myocardial infarction includes nontransmural as well as transmural myocardial infarction. Elevated levels of 2 or more enzymes including serum glutamic oxalacetic transaminase, lactic dehydrogenase, and creatinine phosphokinase to at least twice the upper limit of normal for our laboratory within 72 hours of the onset of symptoms were required for diagnosis.

All patients received routine coronary care which included auscultation of the heart at least twice daily. A diagnosis of postmyocardial infarction pericarditis was established when the patient noted pleuropericardial pain and a definite pericardial friction rub was audible. We did not include patients with a friction rub alone in order to avoid false diagnoses caused by chest wall motion against the stethoscope. Information on anticoagulation during hospitalization and all other clinical data were prospectively gathered on a computerized data form which is completed for every patient with acute myocardial infarction.

Information concerning the presence or absence of Dressler's syndrome was obtained by questionnaires that were completed by the patient's referring physician. This information was used, in addition to the prospectively gathered information obtained during the patient's hospitalization, to determine the precise incidence of complications from the time of admission to 6 months after myocardial infarction. The questionnaire requested information on the patient's status, therapy including anticoagulation, and the presence or absence of Dressler's syndrome. If a diagnosis of Dressler's syndrome was made, the physician was asked to indicate the presence or absence of specific abnormalities which included temperature elevation, pleuropericardial pain, pleuropericardial rub, elevated eosinophilic sedimentation rate (>20 mm/h), elevated white blood cell count (>10,000/mm^3), pneumonitis, and x-ray evidence of cardiomegaly.

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Using Dressler's original criteria,[2] Dressler's syndrome was suspected when a febrile period after myocardial infarction lasted longer than 1 week and was accompanied by pleuropericardial pain, or when fever and chest pain recurred. The diagnosis was confirmed when a pericardial rub was audible for 3 days or longer or when it appeared late in the course of the illness.

Results

From January 1, 1980 through December 31, 1980, 282 patients with documented myocardial infarction were admitted to our coronary care unit.

Early postmyocardial infarction pericarditis was seen in 18 patients (6.4%) during the initial hospitalization. Twelve of these patients had anterior and 6 had inferior wall myocardial infarction. In each case a pericardial rub was heard on the second or third postmyocardial infarction day, lasted only 1 or 2 days, and did not recur. No evidence of pneumonitis or significant pericardial effusion was noted on chest x-ray. Six of these patients had echocardiograms that also failed to show significant pericardial effusion. Six of the patients received parenteral steroids for the treatment of pericarditis, while the remainder were treated with salicylates or other anti-inflammatory agents. Five patients died during hospitalization.

Questionnaires were returned on 229 patients who were discharged alive from our coronary care unit after myocardial infarction. Sixteen questionnaires indicated that the patient had died within 6 months of discharge and 4 patients were lost to follow-up study. Dressler's syndrome was thought to be present in only 2 patients by the referring physician. We did not believe that this diagnosis was substantiated in either case. One patient had pleuropericardial pain and a temperature elevation after insertion of a temporary pacemaker. A pericardial rub was never documented and the temperature promptly returned to normal after antibiotic therapy. The second patient also had no documentation of a pericardial rub or temperature elevation.

Anticoagulant therapy was used in 149 patients (53%) during the initial hospitalization. One hundred forty-four patients (51%) were receiving heparin and only 5 patients (2%) received coumadin; 133 patients (47%) received no anticoagulants.

Discussion

To study the incidence of Dressler's syndrome, it is necessary to define it precisely and to carefully distinguish it from the more common early postmyocardial infarction pericarditis.

Dressler[2] estimated that this complication occurred in 3 to 4% of myocardial infarctions, whereas Broch and Ofstad[4] noted only a 1% incidence. The clinical features of Dressler's syndrome include fever, pleuropericardial chest pain, evidence of pneumonitis, and a tendency to recur.[2,5] Because many of these features are seen with early postmyocardial infarction pericarditis, it is important to look for features that are specific for Dressler's syndrome. Dressler[2] noted that the rub occurred late in the syndrome he described. Most rubs occurred between the 2nd and 11th weeks and persisted 3 days to many weeks. The specificity of a late occurring rub has recently been questioned. Kossowsky et al[6] described 5 patients with Dressler's syndrome within 1 week after myocardial infarction. They based their diagnosis on the finding of pericardial fluid which they believe does not occur with early postmyocardial infarction pericarditis. Because the time of onset of pericarditis is not specific, the persistence of pericarditis, recurrence, and presence of pericardial effusion are probably the best indicators of Dressler's syndrome. We were unable to find even 1 patient with characteristics of this type of persistent and recurrent pericarditis. In addition, none of our patients with early postmyocardial infarction pericarditis had evidence of significant pericardial effusion judged by either echocardiogram or conventional chest x-ray.

The incidence of early postmyocardial infarction pericarditis varies from 6.8 to 16%[7–11] and depends largely on the frequency of examination. This type of pericarditis usually occurs on the second to fourth postmyocardial infarction day and lasts only 1 or 2 days. There is frequently a slight temperature elevation which is usually associated with myocardial necrosis. Pneumonitis does not commonly occur and significant pericardial effusion is not found.[5,9] Our incidence of 6.4% and the clinical picture we observed are consistent with this description.

Kossowsky et al[12] believe that the separation of pericarditis after myocardial infarction into 2 varieties is "arbitrary and artificial." They feel that patients with Dressler's syndrome have all had early postmyocardial infarction pericarditis and are simply a subgroup in whom prolonged and severe pericarditis develops. Other investigators[7,8,11] have described a series of patients with early postmyocardial infarction pericarditis, in a small proportion of whom Dressler's syndrome later developed. We believe that 2 definite forms of pericarditis did previously exist.

Various causes of Dressler's syndrome have been proposed and must be considered when looking to explain its decreased incidence. Dressler et al[13] believed that inflammatory complications of myocardial infarction such as pericarditis were allergic in nature and represented a hypersensitivity reaction to autoantigens resulting from myocardial necrosis. Heart muscle antibodies have been found in patients after myocardial infarction.[14] Some studies report this more commonly in patients with Dressler's syndrome,[15] leading to the theory that myocardial infarction releases cardiac substances that behave as autoantigens and cause the clinical syndrome.[16] Liem et al[17] found antibodies to heart muscle in 12% of patients with myocardial infarction but none had evidence of Dressler's syndrome. They conclude that heart muscle antibody cannot be considered specific for the development of Dressler's syndrome. Kossowsky et al[12] also believe that there is no evidence for an autoimmune mechanism. Burch and Colcolough[18] suggest a viral cause, with the trauma of myocardial infarction reactivating latent or dormant viral infection.

Dressler[2] postulated that anticoagulant therapy might play a role in etiology by causing leakage of blood into the serous cavities which would cause signs of pericarditis. He also noted that 75% of his patients were receiving anticoagulants and 25% were not. Anticoagulation at the time of Dressler's original report consisted of oral bishydroxycoumarin which was usually started with a high loading dose. The difference in anticoagulant use and incidence is an important finding in our study. Although 53% of our patients were being given anticoagulants, heparin was used almost entirely, which is much easier to control and less likely to cause significant pericardial bleeding. An extensive area of pericardial irritation, therefore, is less likely to occur.

Difference in observer awareness is a possible explanation of our incidence of Dressler's syndrome. We believe that this is unlikely, because Dressler's syndrome was originally described at this Medical Center and our level of awareness of this syndrome is high. Davidson et al[19] stated that the diagnosis should present little difficulty provided the physician is aware of its existence.

Therapy of early postmyocardial infarction pericarditis may affect the incidence of Dressler's syndrome. Several investigators[7,8,11] noted that their patients with Dressler's syndrome also had early postmyocardial infarction pericarditis. Dressler's syndrome may be merely a continuing pericarditis that occurs in a small subgroup of patients. Six of our 16 patients with early pericarditis were treated with steroids, whereas the remainder were aggressively treated with salicylates or other anti-inflammatory drugs.

We conclude that Dressler's syndrome has decreased in incidence and perhaps disappeared. This decrease does not appear to be explained by decreased physician awareness or changes in coronary care unit procedure. We suggest that it most likely related to decreased use of oral anticoagulants and to more aggressive treatment of early postmyocardial infarction pericarditis.

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Spontaneous Changes in Thallium-201 Myocardial Perfusion Imaging After Myocardial Infarction

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To examine regional myocardial perfusion after myocardial infarction, 26 patients underwent exercise electrocardiographic testing with thallium-201 myocardial perfusion imaging 3 weeks and 3 months after infarction. At 3 weeks, 9 of 26 patients (35%) had myocardial ischemia by exercise electrocardiographic testing, whereas 18 of 26 (69%) had ischemia by thallium-201 imaging. The thallium-201 scintigrams were scored by dividing each image, in 3 views, into 5 segments, using a 5-point scoring scheme. The exercise thallium-201 score was 44.3 ± 1.2 and increased to 47.3 ± 1.2 in the redistribution study ($p < 0.001$). Three months after infarction, although there was a significantly greater rate-pressure product which would predict a larger ischemic defect and a decrease in the stress thallium-201 score, the stress score was improved (48.3 ± 1.1, $p < 0.001$). The redistribution score was similar, that is, 48.9 ± 1.0. The improvement in thallium-201 myocardial perfusion was associated with a loss of stress-induced ischemia in 8 patients (30%). These results indicate that spontaneous improvements in thallium-201 myocardial perfusion imaging may occur after myocardial infarction.

The first few weeks after myocardial infarction are characterized by an improvement in exercise capacity and myocardial oxygen demands.[1-3] Various explanations, including a "training effect" with peripheral adaptation and neurally mediated reflex cardiac changes, have been suggested to explain this phenomenon.[3] However, some investigators speculate that there may be an improvement in myocardial oxygen supply,[1,4] possibly through collateral channels that are commonly seen after infarction. In this respect, Borer et al[4] postulated that improved myocardial perfusion through collateral formation may explain improvement in left ventricular function and reserve seen in some patients within the first year after infarction.

Thallium scintigraphy in the early postinfarction period accurately predicts multivessel disease and jeopardized myocardium.[5] However, serial studies of myocardial blood flow in the weeks after myocardial infarction have not previously been performed. To further explore changes in myocardial perfusion in the early convalescent phase after myocardial infarction, we studied 26 patients serially 3 weeks and 3 months after infarction with thallium-201 myocardial perfusion imaging.

Methods

Twenty-six patients with acute myocardial infarction were evaluated prospectively. All patients gave written informed consent on entry into the study and before each exercise testing session. There were 24 men and 2 women aged 35 to 68 years (mean 55 ± 8.8). Six patients had a previously documented myocardial infarction. All patients fulfilled the following diagnostic criteria for acute infarction: an evolutionary serum enzyme pattern consistent with myocardial necrosis including an elevation in the creatine kinase MB isoenzyme fraction, and at least 1 of the following 2 criteria: retrosternal chest pain consistent with myocardial ischemia lasting at least 30 minutes, or electrocardiographic changes. The diagnostic electrocardiographic changes of transmural myocardial infarction included S-T segment elevation, T-wave inversion, and development of Q waves of at least 40 ms in duration and 25% or greater than the R-wave amplitude in the same lead. The electrocardiographic criteria for nontransmural myocardial infarction consisted of S-T segment depression of

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T-wave inversion persisting at least 24 hours without the development of pathologic Q waves.

With the foregoing electrocardiographic criteria for location and type of infarction, 5 patients (20%) had an anterior transmural infarction, 13 patients (50%) an inferior transmural infarction, and 8 patients (30%) nontransmural infarction.

Patients excluded from this study included (1) those older than 69 years; (2) those with postinfarction angina at rest or of a changing nature; (3) those with hemodynamically significant valvular heart disease suspected on clinical and noninvasive examination; (4) those with uncontrolled hypertension (blood pressure greater than 170/100 mm Hg) despite medical therapy; (5) those with complications related to myocardial infarction such as clinical congestive heart failure despite medical therapy or pulmonary embolism; and (6) those with an exercise-limiting musculoskeletal abnormality.

Each patient was classified according to the Killip and Kimball classification[6] and to the coronary prognostic index of Norris et al.[7] All patients underwent enzymatic estimation of infarct size as determined by serial total creatine kinase (CK) curves. Blood samples were obtained on admission and every 4 hours during the first 72 hours. Total CK was assayed spectrophotometrically by the method of Rosalki.[8] The infarct size was estimated by analysis of serial CK determinations as described by Shell et al.[9] Infarct size was corrected for body surface area and expressed as an infarct size index (ISI) in CK-g-Eq/m^2.

Three-week assessment: Approximately 3 weeks (24.4 ± 3.9 days) after myocardial infarction, each patient was interviewed and examined by a physician. The patients then underwent symptom- or sign-limited treadmill exercise testing using a modified Naughton protocol. The end points of exercise were: (1) development of symptoms that increased, leading directly to termination of effort, that is, chest pain, dyspnea, fatigue, leg cramps, or dizziness; (2) development of signs such as decrease in systolic blood pressure of at least 10 mm Hg below the peak value obtained at a previous stage of exercise or the appearance of ventricular tachycardia (3 successive ventricular premature beats). At peak exercise, 1.5 mCi of thallium-201 (New England Nuclear, North Billerica, Massachusetts) was injected intravenously and exercise was continued, when possible, for an additional 60 seconds. Twelve-lead electrocardiograms and blood pressure measurements were recorded at rest, before exercise testing, and at the end of each 3-minute stage of exercise and at 1, 2, 3, 5, and 7 minutes after exercise (or until the electrocardiogram returned to the preexercise state).

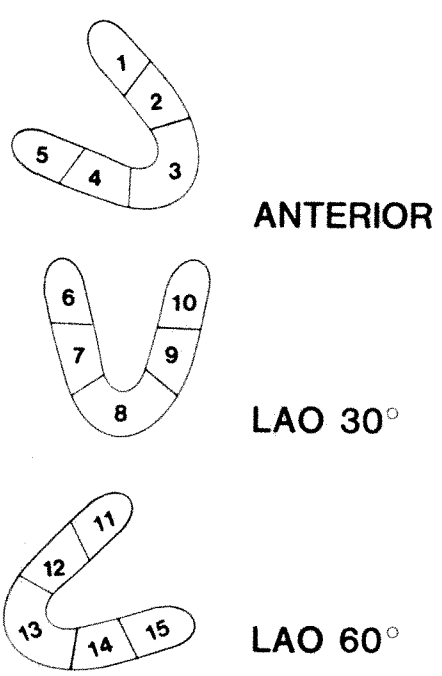

FIGURE 1. Diagram illustrating the thallium study scoring system. Each of the 3 projections (anterior, LAO 30°, and LAO 60°) was divided into 5 segments, resulting in 15 segments (as numbered) in each study. Each segment was scored from 0 to 4, as follows: 0 = severely abnormal, 1 = moderately abnormal, 2 = mildly but definitely abnormal, 3 = equivocally abnormal, and 4 = normal activity. LAO = left anterior oblique.

After the recovery period, myocardial imaging of thallium-201 was recorded using a scintillation camera (Searle Pho/Gamma IV, Des Plaines, Illinois) set for 80 keV with a low energy, all-purpose parallel hole collimator. Data collection was begun in all cases within 10 minutes of radioactive tracer injection. Data were collected in each of the 3 projections (anterior, 30° left anterior oblique, and 60° left anterior oblique). Between 250,000 and 300,000 counts were collected per projection. All images were collected using a Polaroid® photographic record obtained directly from the camera's cathode ray display. In addition, the data were collected and viewed on a dedicated nuclear medicine computer (A^2, Medical Data Systems, Ann Arbor, Michigan). Thallium imaging and data collection were repeated 4 hours after exercise, as aforementioned, to assess redistribution of isotope.[10]

Exercise and postexercise electrocardiograms were analyzed for a positive or negative response. A positive response was defined as either S-T segment horizontal or downsloping depression of 1.0 mm 0.08 second after the J point or 1.0 mm S-T segment elevation above baseline electrocardiogram for the corresponding leads.

Thallium-201 images were independently assessed semiquantitatively by 2 experienced interpreters unaware of the patient's history and electrocardiographic exercise test results. Each projection was divided into 5 regions of interest and perfusion in each region scored from 4 (normal) to 0 (severely abnormal) (Fig. 1). In cases of disagreement, a consensus score was determined. The final score of each projection was tabulated and a total score, using all 3 projections, was derived. A normal study score was 60. The immediate postexercise images were compared with the 4-hour postexercise images and the perfusion in each region was scored as just described. The thallium study was defined as being representative of an ischemic response if a defect present on the immediate postexercise study became smaller or disappeared on the 4-hour postexercise (rest) study and the total score of the rest study was 2 or more points greater than the immediate postexercise study.

With this thallium scoring system the mean interobserver variability determined by having 2 observers independently score 71 scans was 1.2 ± 1.1 scoring points. In addition, this semiquantitative scoring system correlates well with a computer-derived scoring system.[11,12]

Three-month assessment: At approximately 3 months (mean 90.0 ± 4.7 days), each patient was reexamined, reinterviewed, and then subjected to a symptom- or sign-limited treadmill exercise test using the Bruce exercise protocol. Electrocardiographic recordings and thallium-201 injection with subsequent postexercise and rest studies were performed and analyzed as in the 3-week postmyocardial infarction studies.

TABLE I Individual Patient Data for Electrocardiographic (ECG) and Thallium Testing

						3-Week Assessment						3-Month Assessment					
		MI					ETT			Thallium-201 Score			ETT			Thallium-201 Score	
Case	Age (yr) & Sex	Type	Location	ISI	Killip Class	Medications	RPP	METS	ECG Ischemia	E	R	Medications	RPP	METS	ECG Ischemia	E	R
1	49M	NTM	Inf	3	I	0	17.4	8	−	54	53	0	19.2	18	−	54	56
2	68M	TM	Inf	28	II	Prop, N	13.8	6	−	39	38	Prop, N	10.3	8	−	44	47
3	58M	TM	Inf	19	I	0	19.8	8	−	46	52	0	33.1	18	−	51	51
4	50F	TM	Ant	19	I	Dig	11.5	7	−	38	40	Dig	21.0	10	−	44	44
5	66M	TM	Inf	21	I	Dig	14.7	4	+	36	38	Dig	18.0	9	+	36	41
6	64M	TM	Ant	11	I	0, N	13.5	8	+	49	54	0, N	24.3	16	+	49	51
7	65M	TM	Inf	7	I	0	18.3	3	−	40	49	0	17.4	8	−	40	42
8	53M	TM	Inf	33	II	Dig	11.7	4	−	38	42	Dig	16.8	14	+	39	40
9	58M	TM	Ant	45	I	Dig	12.5	4	−	39	38	Dig	14.1	15	+	44	47
10	59M	TM	Inf	7	I	Prop, N	12.4	8	+	51	55	Prop, N	13.1	10	−	55	55
11	57M	NTM	Inf	14	I	Prop	17.1	7	+	52	50	Prop	18.0	10	+	50	52
12	39M	TM	Inf	14	I	0	21.1	7	−	47	49	0	33.2	14	−	55	51
13	67M	TM	Ant	41	II	Dig, Prop, N	10.6	3	−	34	45	Dig, Prop, N	8.7	3	−	44	44
14	46M	TM	Inf	33	I	0	11.8	6	−	37	45	0	30.2	10	−	45	47
15	35M	NTM	Ant	5	I	0	22.5	10	−	53	53	0	22.8	11	−	53	53
16	50M	NTM	Ant	17	I	0	20.9	5	+	48	53	0	24.7	9	+	46	50
17	48M	TM	Inf	5	I	0	17.8	7	−	43	43	0	30.5	9	−	50	48
18	57M	TM	Inf	20	I	0	14.4	8	−	44	48	0	29.2	16	−	51	49
19	66M	NTM	Ant	27	I	Prop, N	18.4	5	+	46	54	Prop, N	19.4	7	+	52	51
20	44M	NTM	Ant	9	I	N	11.0	7	−	53	58	0	25.7	16	−	58	59
21	61F	NTM	Inf	5	I	Prop, N	13.5	5	+	46	49	Prop, N	15.6	9	+	55	49
22	57M	TM	Inf	31	II	Dig	23.6	3	−	37	42	Dig	30.0	9	+	43	45
23	62M	TM	Ant	4	I	Dig, Prop	14.7	4	+	48	50	Dig, Prop	14.4	7	+	52	53
24	62M	TM	Inf	10	I	Prop, N	19.0	4	+	42	52	Prop, N	18.5	8	+	49	53
25	49M	TM	Inf	21	I	0	20.9	6	−	41	39	0	25.5	10	+	41	41
26	46M	NTM	Ant	41	I	Prop, N	12.7	4	−	40	39	0, N	19.2	11	−	45	45

Ant = anterior; Dig = Digoxin; E = exercise; ETT = exercise treadmill testing; Inf = inferior; ISI = infarct size index (CK-g-Eq/m^2); N = nitrates; 0 = no medications; Prop = propranolol; MI = myocardial infarction; NTM = nontransmural; R = redistribution; RPP = rate-pressure product (mm Hg/min $\times 10^3$); TM = transmural.

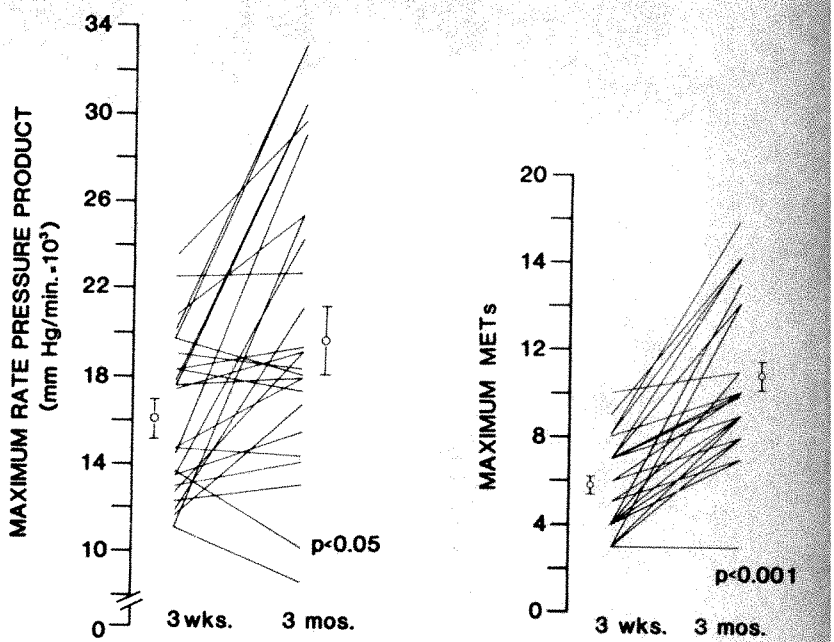

FIGURE 2. Both the maximal rate-pressure product and exercise work load for the entire study population increased significantly at 3 months compared with 3 weeks.

The thallium-201 studies obtained at 3 weeks were also compared with those at 3 months. As just described, semiquantitative assessment of perfusion alterations between corresponding sites of comparable projections at 3 weeks and 3 months was made immediately and after redistribution. Throughout the study, no attempt was made to standardize or influence medical therapy except to withhold the administration of any nitrates 90 minutes before each exercise test.

Analysis of data: Intragroup variables at 3 weeks and 3 months were compared using the paired t test. Intergroup variables at 3 weeks and 3 months were compared using the unpaired t test. Chi-square analyses and Fisher exact test were used to compare inter- and intragroup differences in the type and location of myocardial infarction and also to compare changes in ischemic response between those at 3 weeks and those at 3 months. All values given in the text are expressed as mean ± standard error of the mean.

Results

Individual patient data and results of exercise electrocardiographic and thallium testing are summarized in Table I. All patients had myocardial infarction and were categorized as Killip class I (22 patients) or Killip class II (4 patients). The mean Norris index for the group was 5.5 ± 0.4. The mean infarct size was 18.9 ± 2.6 CK-g-Eq/m^2. The patients were discharged from the hospital after 12.9 ± 0.9 days.

Three-week assessment: The study patients exercised to a mean work load of 5.9 ± 0.4 multiples of resting energy expenditure (METs), achieving a maximal rate-pressure product of 16.2 ± 0.7 mm Hg/min × 10^3 (Fig. 2).

During exercise, chest pain consistent with angina developed in 3 patients (12%), and 9 patients (35%) had positive electrocardiographic changes of myocardial ischemia. With thallium-201 scintigraphy, 18 patients (69%) had evidence of myocardial ischemia.

All patients demonstrated defects on redistribution rest thallium-201 studies compatible with myocardial infarction. All of the patients with myocardial ischemia on thallium-201 scintigraphy had evidence of ischemia on exercise studies in the peri-infarct areas. However, in addition, 8 patients (40%) with myocardial ischemia on thallium-201 scintigraphy also had evidence of ischemia on exercise studies, which occurred in a remote site in a separate vascular region from the rest defects. The exercise thallium-201 perfusion score was 44.3 ± 1.2 and increased in the redistribution rest study to 47.7 ± 1.2 ($p < 0.001$) (Fig. 3).

Medication at the time of the initial study included digoxin (7 patients), beta-blocking drugs (11 patients), and nitrate compounds (9 patients). Four of the patients taking beta-blocking drugs had been on this medication before their study infarction.

Three-month assessment: No coronary events were recognized between the 3 week and 3 month assessments. The study patients achieved a work load of 10.8 ± 0.8 METs, which was significantly greater than that of the 3 week assessment ($p < 0.001$). Similarly, a higher maximal rate-pressure product was achieved (20.0 ± 1.7 mm Hg/min ×10^3) ($p < 0.05$) (Fig. 2).

During exercise, 4 patients (15%) experienced angina. In 3 of these patients angina had developed at the 3-week exercise session. Myocardial ischemia was thought to be present on the basis of electrocardiographic evaluation in 13 patients (50%). Stress thallium-201 perfusion imaging demonstrated ischemia in 10 patients (38%), in all in an area adjacent to the infarction. In addition, 3 of these patients (15%) had evidence of remote ischemia. The stress thallium-201 score was significantly improved at 3 months (48.3 ± 1.1, $p < 0.001$) (Fig. 3 and 4). However, the redistribution thallium-201 score at 3 months, 48.9 ± 1.0, was not significantly

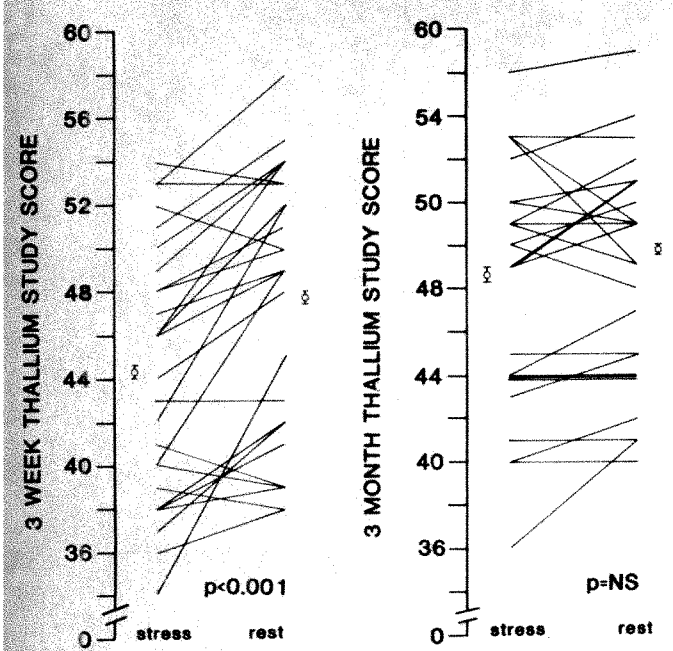

FIGURE 3. The thallium rest and stress study scores at both 3 weeks and 3 months for the entire study population are illustrated. There was a significant difference between the rest and stress scores at 3 weeks but not at 3 months.

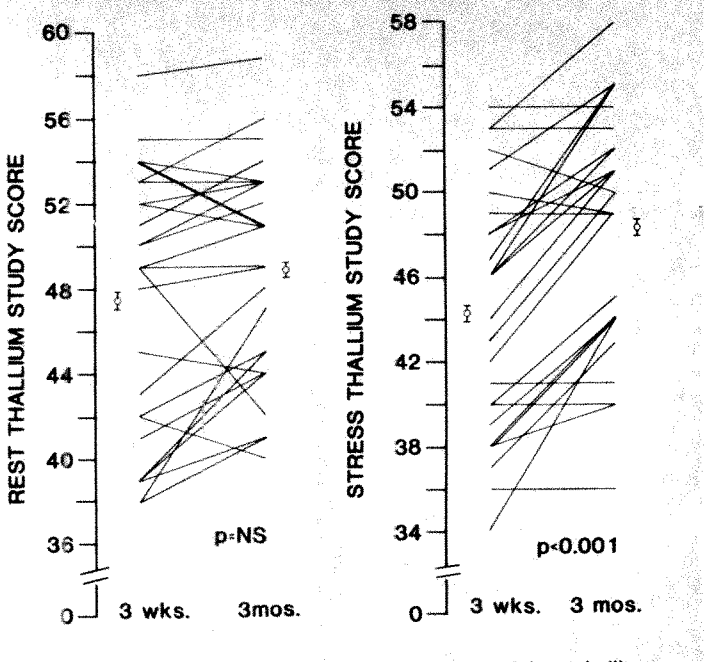

FIGURE 4. There was no signicant difference in the serial rest thallium study scores between 3 weeks and 3 months. However, a significant increase in the serial stress thallium study scores for the entire study group was seen.

changed compared with that at 3 weeks (Fig. 3 and 4). An example of improvement in the thallium-201 scintiscan is illustrated in Figure 5.

Few medication changes were made in the 3-week to 3-month interval. One patient had discontinuation of propranolol and 1 patient of nitrate therapy, whereas 2 other patients were started on nitrates.

Thallium perfusion changes: On the basis of changes in myocardial perfusion, 2 groups were identified: Group I consisted of 18 patients (69%) who demonstrated an improvement in thallium perfusion between 3 weeks and 3 months, and Group II included 8 patients (31%) who showed no such improvement.

No significant differences between the 2 groups were noted in terms of age; previous infarction; Killip and Norris indexes; type, location, and size of myocardial infarction; and medications at the time of study. Nine patients in Group I received beta-blocking drugs throughout the study as compared with 1 patient in Group II.

In Group I the exercise thallium-201 score was 43.2 ± 1.2 at 3 weeks and increased to 49.0 ± 1.3 ($p < 0.001$). An improvement in the redistribution thallium-201 study also occurred between that at 3 weeks and that at 3 months (from 46.7 ± 1.4 to 49.0 ± 1.3 [$p < 0.01$]). In Group II the exercise thallium score at 3 weeks was 46.8 ± 2.4 and was unchanged at 3 months (46.7 ± 2.2, p = NS). Similarly, no change occurred in the redistribution thallium-201 image between 3 weeks and 3 months (49.1 ± 2.4 to 48.6 ± 2.1 [p = NS]).

Group I patients had a significant increase in both the work load developed (5.7 ± 0.4 to 10.7 ± 0.9 METs [$p < 0.001$]) and the maximal rate-pressure product (15.3 ± 0.9 to 21.3 ± 1.9 mm Hg/min × 10^3 [$p < 0.001$]) from the 3-week to the 3-month exercise testing session. Group II patients also had a significant increase in the work load developed on the 3-month exercise test (6.5 ± 0.8 to 11.0 ± 1.3 METs [$p < 0.01$]). However, Group II patients did not have a significant increase in the maximal rate-pressure product between tests (18.0 ± 1.1 to 18.4 ± 2.6 mm Hg/min × 10^3).

Seven patients who demonstrated an ischemic response at 3 weeks but none at 3 months on thallium-201 imaging were taking beta-blocking medication. All of these patients were in Group I.

Discussion

Thallium-201 myocardial perfusion imaging is a technique to evaluate regional myocardial blood flow[13] that has proved useful in detecting, localizing, and sizing myocardial infarction and surrounding jeopardized ischemic myocardium.[14–17] Wackers et al[14] demon-

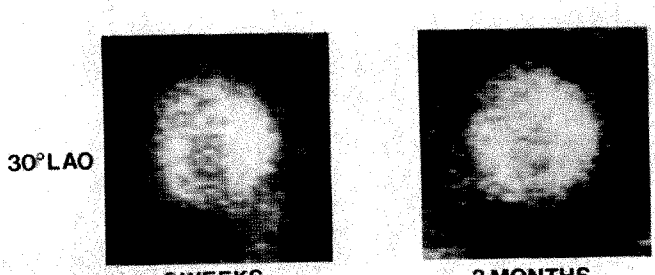

FIGURE 5. Serial thallium stress images of a Group I patient, illustrating improved perfusion in the inferoapical region at 3 months (**right**) compared with 3 weeks (**left**).

strated that thallium defects diminish in size in the first few hours and days after myocardial infarction. Regression of ischemia and possible formation of collaterals were suggested as possible explanations for this phenomenon. Our study was designed to further investigate myocardial perfusion in the convalescent phase of myocardial infarction and to document serial changes that occur in the first 12 weeks after infarction.

Our results indicate that myocardial perfusion assessed by thallium scintigraphy may improve between 3 weeks and 3 months after myocardial infarction, suggesting spontaneous improvement in regional myocardial flow in the weeks after infarction.

Thallium imaging is a highly reproducible technique for examining myocardial perfusion abnormalities.[18] In serial studies, increasing the exercise workload and rate-pressure product produces greater perfusion abnormalities in patients with coronary disease, thus increasing the sensitivity of the test.[18] By contrast, our study indicates an improvement in myocardial perfusion in 69% of our study patients at 3 months, despite significantly greater workloads and rate-pressure products. The fact that improved thallium-201 perfusion was demonstrated despite significantly greater rate-pressure products, and hence increased myocardial oxygen demands, underscores the improvement in regional myocardial blood flow in these patients.

This improved myocardial perfusion is best explained by some form of a revascularization process that occurs in the first few weeks after infarction. Collateral vessels modulate infarct size after coronary occlusion in dogs[19]; however, their role during infarction in man remains poorly understood. Angiographic studies show that collateral vessels occur commonly in the first year after infarction.[20,21] Moreover, Rigo et al[12] demonstrated that collateral vessels may account for normalization of the thallium scans and protection from stress-induced ischemia. Other investigators demonstrated improvement in myocardial perfusion after revascularization with coronary artery bypass grafting[22–25] or percutaneous transluminal coronary dilatation.[26] Thus, the improved regional myocardial perfusion that we observed is consistent with revascularization, presumably through collaterals or recanalization of vessels,[27] in the first few weeks after infarction.

Previous studies[28–30] have suggested that myocardial perfusion may improve in some patients after myocardial infarction. These investigators[28–30] noted normalization of thallium-201 scintigrams after myocardial infarction. Verani et al[30] demonstrated that periinfarction ischemia occurs commonly with chronic infarction and that other areas of prior necrosis apparently reestablish vascularity sufficient to afford total redistribution of thallium-201 on delayed postexercise imaging. However, none of these reports documented this improvement using serial thallium-201 myocardial perfusion studies.

When compared with stress electrocardiographic testing, thallium scintigraphy in our study was more sensitive in detecting ischemia at 3 weeks postmyocardial infarction. Ischemia, as assessed by thallium, was always contiguous to the area of infarction, but in 40% of patients additional remote ischemia in a separate vascular region suggested multivessel disease.[5] As a result of the improved perfusion between 3 weeks and 3 months, stress electrocardiography was equally as sensitive as thallium imaging in detecting ischemia at 3 months postinfarction. This spontaneous improvement in myocardial perfusion eliminated stress-induced residual ischemia in 30% of the study patients. Thus, the development of increased perfusion may have a protective effect against recurrent ischemic episodes.

Similar to previous reports,[1–3] exercise capacity and peak rate-pressure product in our patients improved in the interval between 3 weeks and 3 months postmyocardial infarction. Haskell and DeBusk[3] speculated that gradual waning of a reflex arising from dyskinetic myocardial segments or a "training effect" may be responsible for this improvement. However, Wohl et al[1] suggested that the improved rate-pressure product and exercise capacity could best be explained by an improvement in myocardial oxygen supply. Our data demonstrating improved myocardial perfusion support this suggestion.

Previous studies have shown that myocardial function can improve after myocardial infarction.[4,31,32] Recently Borer et al,[4] using radionuclide angiography, demonstrated spontaneous improvement in ventricular function within the 1st year after infarction in 17 of 40 patients who were a subgroup of patients with less damage and more viable myocardium and a resting ejection fraction greater than 40%. Borer et al[4] suggested that this improvement in ventricular function was related to a possible improvement in myocardial oxygen supply because of progressive development of collateral vessels. Our data demonstrating a spontaneous improvement in myocardial perfusion after infarction supports this hypothesis. Conceivably, then, myocardial function, particularly with stress intervention, improves in the convalescent phase after infarction because of improved perfusion.

There are certain limitations in our study. All patients had myocardial infarction in Killip class I and II and were therefore highly selected. The improved perfusion we noted after infarction does not therefore necessarily apply to other subgroups. In addition, our study was designed to be noninvasive and therefore we do not have angiographic correlates.

In conclusion, our results indicate that thallium scintigraphy may be used serially after infarction to detect improvement in perfusion which occurs in some patients after uncomplicated myocardial infarction. This improved perfusion produces resolution of residual ischemic myocardium and may thus have a protective effect. Moreover, this increased perfusion may be an important factor accounting for improvement in ventricular function in some patients in the first year after infarction. Thus, the effect of exercise programs and of drug and surgical interventions on myocardial perfusion must be interpreted cautiously within the first 12 weeks after myocardial infarction.

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Assessment of the Use of the Age- and Sex-Specific United States Population as a Control Group for Analysis of Survival in Coronary Artery Disease

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The use of the age- and sex-specific U.S. population as a control group for analysis of survival in coronary artery disease was assessed. Population-based survival rates were calculated for nonsurgically treated patients evaluated for coronary artery disease at Duke University Medical Center. Survival of the overall group of medically treated patients with significant coronary artery disease was lower than the corresponding age- and sex-specific U.S. population rates. However, survival of patients with significant disease who had normal left ventricular contraction and stable chest pain was similar to the age- and sex-specific population survival rates. Both the observed survival and the population-based survival estimates for patients with normal left ventricular contraction and stable pain were lower than the survival of patients with normal coronary arteriograms. Even after deaths from ischemic heart disease are eliminated from the population rates, survival of patients with normal coronary arteries exceeded the age- and sex-specific population survival. Because of biases inherent in the selection of patients for cardiac catheterization and the presence of other serious diseases in persons in the general population, the age- and sex-specific U.S. population is not an adequate control group for rigorous analysis of the effect of therapy in coronary artery disease.

With the widespread use of new therapies in coronary artery disease, intense interest in the effects of these therapies on longevity has developed. Randomized and observational studies have clarified the role of specific treatments in particular subgroups of patients. For example, coronary artery bypass surgery prolongs survival in patients with left main coronary disease,[1] and beta-adrenergic blocking drugs prolong survival in some groups of patients after myocardial infarction.[2,3] These studies used concurrent patients for comparison who either were not treated or were given a specified alternative therapy. However, many large series of patients receiving a particular therapy, such as coronary artery bypass grafting, were studied in the absence of a comparable concurrent group of patients who did not receive the therapy.[4,5] In an effort to obtain a group for comparison, expected survival based on the age- and sex-specific U.S. population has been used in some instances.[6,7] The purpose of this study was to examine the use of the age- and sex-specific U.S. population mortality data as a standard against which to compare outcomes in patients with coronary artery disease.

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Methods

Information system and patient population: Since 1969 at Duke University Medical Center, a comprehensive set of data has been collected on every patient undergoing cardiac catheterization.[8] Descriptors of the history, risk factors,

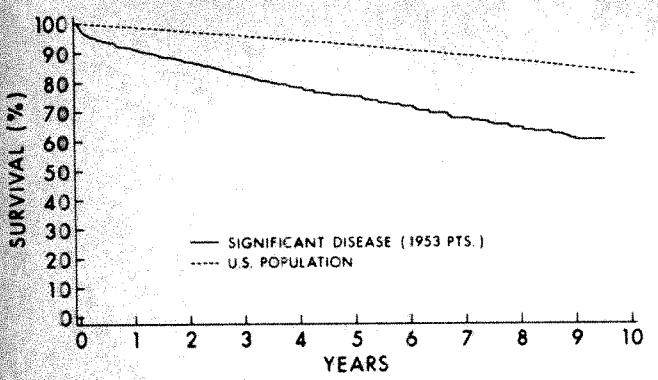

FIGURE 1. Survival in patients with significant coronary artery disease treated nonsurgically and the expected survival for these patients based on the age- and sex-specific U.S. population.

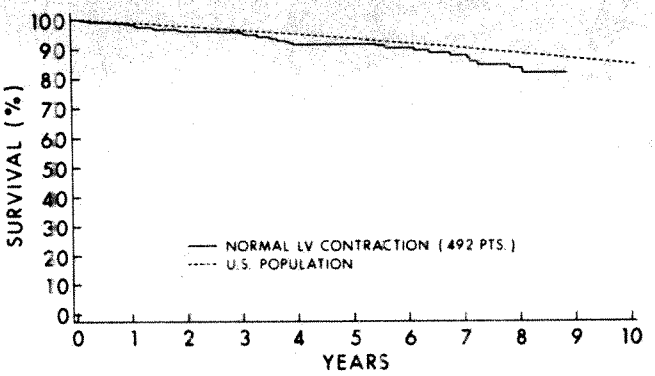

FIGURE 2. Survival in patients with significant coronary artery disease, stable chest pain, and normal left ventricular (LV) contraction and their expected survival based on the age- and sex-specific U.S. population.

physical examination, chest X-ray, electrocardiogram, and cardiac catheterization were recorded prospectively. In patients who underwent exercise testing, ambulatory monitoring, or cardiac imaging, the pertinent data were also collected. Follow-up information on survival status, occurrence of myocardial infarction, hospitalization, and chest pain was obtained at 6 months and 1 year after catheterization and at yearly intervals thereafter. Overall, follow-up study was 99% complete. To date, this information has been collected on 5,700 patients.

In this study, patients with congenital or valvular heart disease other than mitral valve prolapse or mitral regurgitation secondary to ischemic heart disease were excluded. Significant coronary artery disease was defined as ≥75% stenosis of a major coronary vessel (main left, left anterior descending or large diagonal branch, left circumflex or large marginal branch, or right coronary artery). Stable angina was defined as angina that had not been increasing in duration, severity, or frequency in the 6 weeks before cardiac catheterization. Normal left ventricular contraction was defined as the absence of contraction abnormality on the left ventriculogram at cardiac catheterization in the subjective opinion of 3 experienced angiographers.

U.S. population data: In each patient group for which an age- and sex-specific U.S. life table survival curve was calculated, the following procedure was used. For each individual patient, the age- and sex-specific probability of survival at yearly intervals through 10 years from the time of cardiac catheterization was calculated. These individual probabilities were then averaged for all patients in the group to produce population-based life table survival estimates for that particular group. Survival probabilities were calculated for all causes of death and for death from causes other than ischemic heart disease. U.S. age- and sex-specific life table mortality data published in 1975 by the National Center for Health Statistics formed the basis for these calculations.[9,10] These published mortality figures were derived from data of the 1970 population census and actual deaths that occurred in the U.S. from 1969 through 1971. The actual observed mortality experience of the patients was summarized using Kaplan-Meier life table survival estimates.[11]

Results

Figure 1 depicts the overall survival of 1,953 nonsurgically treated patients with significant coronary artery disease compared with the estimated survival based on U.S. population data. All causes of death are included. Overall, patients with significant coronary disease are at increased risk of death compared with the general population. At 1 year after catheterization, survival of patients with coronary artery disease was 91% compared with an estimated 99% 1-year survival based on the age- and sex-specific U.S. population. The 5-year survival of patients with coronary artery disease was 75%, whereas the expected survival based on U.S. population data was 92%.

Survival in 492 patients with normal left ventricular contraction, stable angina, and significant coronary disease treated nonsurgically compared with their expected survival based on age- and sex-specific population data is shown in Figure 2. The survival curves are almost identical. At 1 year the observed survival is 98% and at 5 years the survival is 92%. This figure demonstrates that in patients with significant coronary artery disease treated nonsurgically, the survival of particular subgroups can be similar to the expected survival based on population data.

Figure 3 shows the same curves as Figure 2 along with the survival of the 1,281 patients at our institution with normal coronary arteries and no other significant heart disease at cardiac catheterization. Survival in patients catheterized for chest pain and found to have normal coronary arteries is superior to both the observed survival and to the age- and sex-specific population survival in patients with significant coronary artery disease, normal left ventricular contraction, and stable angina. Thus, although survival in this subgroup of patients compares favorably with population data, we cannot conclude that therapy has eliminated the risk from ischemic heart disease in these patients.

One factor contributing to greater survival in patients with normal coronary arteries when compared with the age- and sex-specific U.S. population is the selection of patients for cardiac catheterization based on the absence of other serious illnesses. To demonstrate this point, survival in patients with normal coronary arteries at catheterization is compared in Figure 4 with their

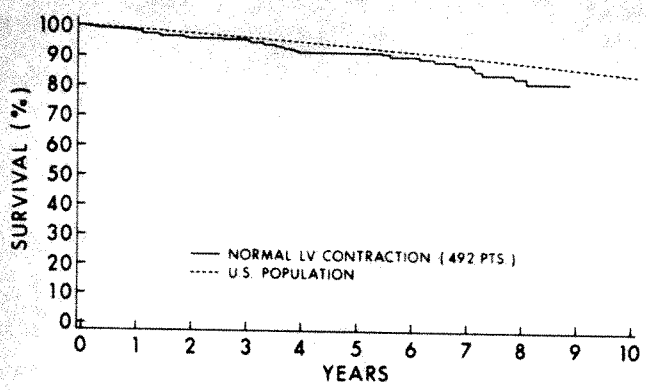

FIGURE 3. Survival in patients with significant coronary artery disease, stable chest pain, and normal left ventricular contraction, their expected survival based on the age- and sex-specific U.S. population, and survival in patients with normal coronary arteries and no other significant heart disease.

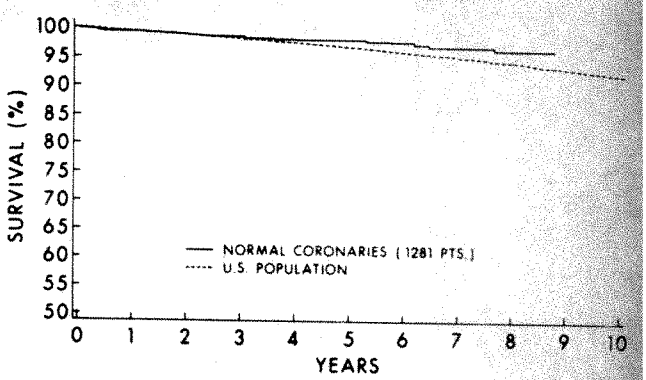

FIGURE 4. Survival in patients with normal coronary arteries and their expected survival based on general population data after excluding deaths from ischemic heart disease.

expected survival based on population data, excluding deaths from ischemic heart disease. Although the difference in survival is small, patients with normal coronary arteries at catheterization have a lower mortality from other causes of death. In our entire population of over 5,700 patients undergoing cardiac catheterization, only 79 deaths were from causes other than ischemic heart disease.

Discussion

Patients with coronary artery disease are at increased risk of death compared with the expected survival of the general U.S. population matched for age and sex (Fig. 1). The patients in this figure represent a wide spectrum of clinical conditions. Of these patients 60% had at least 1 area of abnormal left ventricular contraction and 44% had 3-vessel coronary disease. The manner in which these patients were treated also was not uniform. Most were referred for evaluation to our institution from a broad regional area and returned to the care of their local physician after cardiac catheterization. These patients received a variety of pharmacologic agents and other therapies such as exercise training. Instead of medical therapy, the term nonsurgical therapy provides a better description of the treatment these patients received, because their common feature was their nonsurgical treatment.

Despite decreased survival in the overall group of nonsurgically treated patients, patients selected with particular functional characteristics have a survival comparable to that expected from age- and sex-specific population data (Fig. 2). The particular group of patients with normal left ventricular function and stable angina was chosen only for the purpose of demonstration. Similar results can be demonstrated in patient subgroups defined by other factors such as the number of diseased vessels, history of previous infarction, and exercise test results. The implication of this finding is that clinical, anatomic, and ventricular function status at cardiac catheterization can cause survival to vary widely. Thus, a group of patients with coronary artery disease may have survival similar to the expected survival based on age- and sex-specific U.S. population data even without a particular therapy such as bypass surgery. In institutions in which patients undergo cardiac catheterization early in the course of their disease, a large percentage of patients may have good ventricular function, stable symptoms, and involvement of only 1 or 2 coronary arteries. These patients would be expected to have excellent survival whether treated surgically or nonsurgically.

Figure 3 demonstrates that although a subgroup of patients may have survival equal to the expected survival based on population data, the risk of death from ischemic heart disease has not been eliminated by medical therapy. If the risk of death from ischemic heart disease were eliminated, survival of patients with coronary artery disease should equal that of patients who underwent catheterization and were found to have no coronary artery disease.

The difference in survival between patients with normal coronary arteries and the U.S. population curve can be explained by 2 factors. First, deaths from ischemic heart disease account for a large proportion of deaths in the general population. Obviously, almost no cardiac deaths occurred in our patients with normal coronary arteries. Second, patients undergoing cardiac catheterization are a selected group not only because of chest pain, but also because of the relative absence of other life-threatening illnesses such as cancer and end-stage lung disease.

Figure 4 demonstrates that patients undergoing cardiac catheterization are at lower risk of competing causes of death compared with people in the general population matched for age and sex. Although the observed difference in survival is small after excluding deaths from ischemic heart disease from the population data, it underscores the fact that patients with coronary disease are not strictly comparable to the general population. The selection of patients for catheterization is

based on multiple factors. The absence of other significant life-threatening illnesses may be an important selection bias.

One purpose of comparing the survival of different populations is to gain a general understanding of the outcome of a particular disease. The clinician may approach the patient with coronary disease somewhat differently with the understanding that the survival of selected groups of patients after cardiac catheterization is similar to that of the age- and sex-specific U.S. population. In particular, in the present study, we demonstrated that medically treated patients with good ventricular function and stable chest pain have survival similar to that of the age- and sex-specific population. Therefore, every patient with coronary disease need not feel that death is imminent, and the physician need not always feel that urgent action is needed.

Finally, population mortality data should not be used to determine the efficacy of therapy. Depending on the referral patterns of an institution and the selection process by which patients are given specific therapy, characteristics of the patient series studied may vary widely. We have demonstrated that these characteristics, such as baseline ventricular function and stability of angina, have a profound effect on the relative survival of patients managed medically compared with that of the age- and sex-specific U.S. population. Whether the therapy being investigated is pharmacologic or coronary artery bypass grafting, we cannot assume that if patients who receive the therapy have longevity comparable with age- and sex-specific population data, patients who do not receive the therapy would have a survival less than that of the U.S. population. Therefore, only patient populations in which prognostic characteristics have been carefully documented and adjusted for to insure comparability can be used for comparison to determine therapeutic efficacy. Furthermore, patients having cardiac catheterization are a selected group and are not comparable to the general population with regard to other causes of death.

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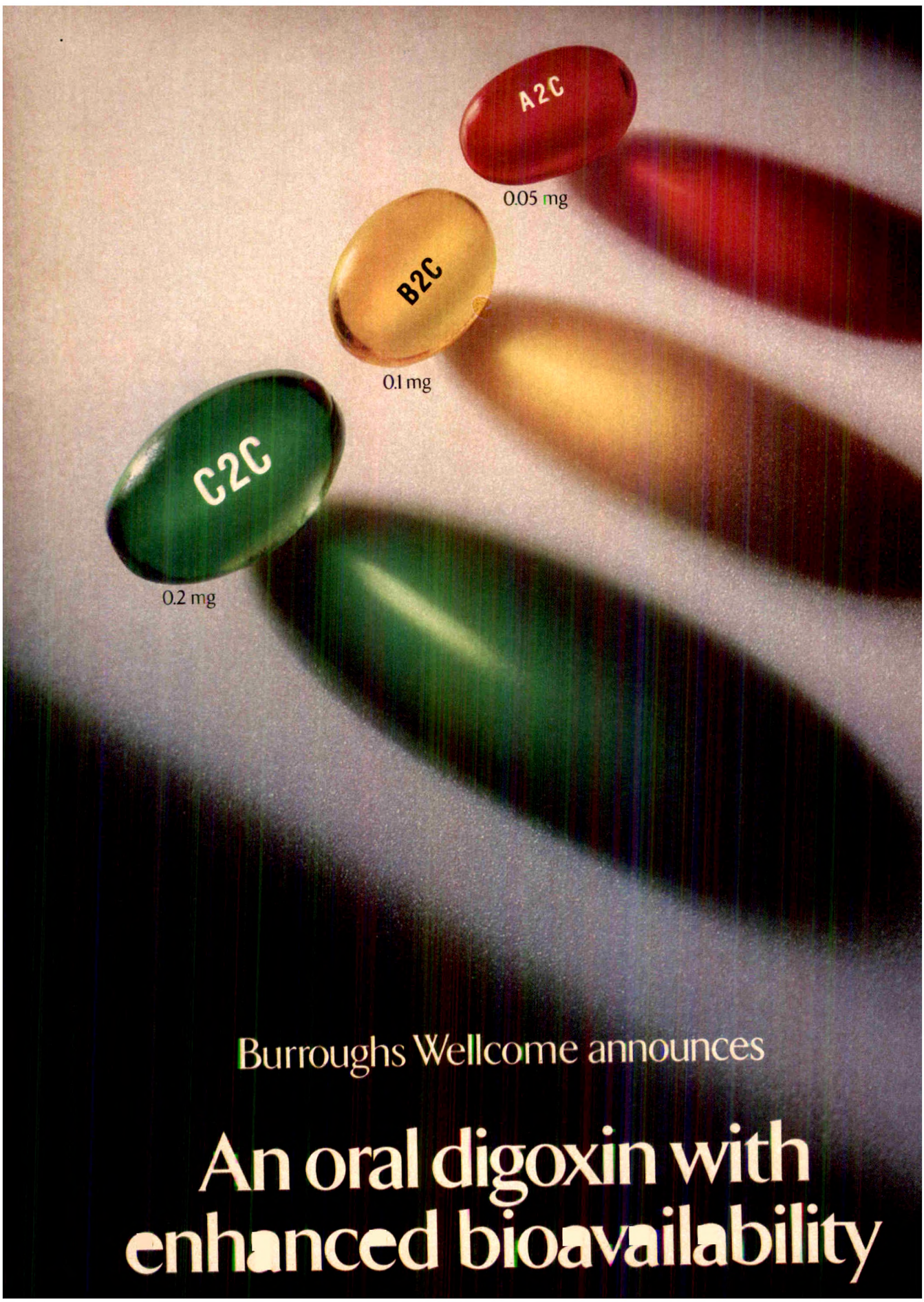

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Digoxin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous fistula, anemia, infection or hyperthyroidism.

Digoxin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies have shown, however, that even though hemodynamic effects can be demonstrated in almost all patients, corresponding improvement in the signs and symptoms of heart failure is not necessarily apparent. Therefore, in patients in whom digoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable renal function or whose potassium levels tend to fluctuate) a cautious withdrawal of digoxin may be considered. If digoxin is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure.

CONTRAINDICATIONS
Digitalis glycosides are contraindicated in ventricular fibrillation.

Any untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin, as is hypersensitivity to digoxin itself. Allergy to digoxin, though rare, does occur. It may not extend to all preparations, and another digitalis glycoside may be tried with caution.

WARNINGS
The use of digoxin or other digitalis glycosides is unwarranted in the treatment of obesity.

Digoxin in soft capsules should be administered in divided daily doses to minimize any potential adverse reactions. Where compliance is considered a problem, single daily dosing may be appropriate.

Anorexia, nausea, vomiting, and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section in complete prescribing information).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary. Careful monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity. Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS
General: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section in complete prescribing information). More time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range," because potassium depletion sensitizes the myocardium to digoxin. Hypokalemia may result from diuretic, amphotericin B, or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see *Treatment of arrhythmias produced by overdosage*, in OVERDOSAGE section).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypocalcemia can nullify the effects of digoxin in man; digoxin may be ineffective until serum calcium is restored to normal.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine causes a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the quinidine dose. Because of the considerable variability of this interaction, digoxin dosage should be carefully individualized.

Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (eg, hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e., sick sinus syndrome), digoxin may worsen sinus bradycardia or sinoatrial block.

In patients with Wolff-Parkinson-White syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Drug Interactions: Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias. *Quinidine* causes a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. *Antacids, kaolin-pectin, sulfasalazine, neomycin,* and *cholestyramine* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Thyroid* administration to a digitalized hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias, because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although *propranolol* and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

ADVERSE REACTIONS
The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section). The overall incidence of adverse reactions has been reported as 5% to 20%, with 15% to 20% being considered serious (1% to 4% of patients receiving digoxin). Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults:
Cardiac—Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease. Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (nodal) rhythm, and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage.

Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances.

Gastrointestinal—Anorexia, nausea, vomiting, and, less commonly, diarrhea are common early symptoms of overdosage. Uncontrolled heart failure may also produce such symptoms.

CNS—Visual disturbances (blurred or yellow vision), headache, weakness, apathy, and psychosis can occur.

Other—Gynecomastia is occasionally observed.

Infants and Children:
Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea, and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Ventricular

arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

OVERDOSAGE Treatment of arrhythmias produced by overdosage

Adults:

Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is necessary if toxic manifestations are not severe.

Potassium salts are commonly used, particularly if hypokalemia is present. Potassium chloride in divided oral doses totaling 3 to 6 grams of the salt (40 to 80 mEq K+) for adults may be given provided renal function is adequate (see below for potassium recommendations in infants and children).

When correction of the arrhythmia is urgent and the serum potassium concentration is low or normal, potassium should be administered intravenously in 5% dextrose injection. For adults, a total of 40 to 80 mEq (diluted to a concentration of 40 mEq per 500 ml) may be given at a rate not exceeding 20 mEq per hour, or slower if limited by pain due to local irritation. Additional amounts may be given if the arrhythmia is uncontrolled and potassium well tolerated. ECG monitoring should be performed to watch for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia. The infusion may be stopped when the desired effect is achieved.

Note: Potassium should not be used and may be dangerous in heart block due to digoxin unless primarily related to supraventricular tachycardia.

Other agents that have been used for the treatment of digoxin intoxication include lidocaine, procainamide, propranolol, and phenytoin, although use of the latter must be considered experimental. In advanced heart block, temporary ventricular pacing may be beneficial.

Infants and Children:

See Adults section (immediately above) for general recommendations for the treatment of arrhythmias produced by overdosage and for cautions regarding the use of potassium.

If a potassium preparation is used to treat toxicity, it may be given orally in divided doses totaling 1 to 1.5 mEq K+ per kilogram (kg) body weight (1 gram of potassium chloride contains 13.4 mEq K+).

When correction of the arrhythmia with potassium is urgent, approximately 0.5 mEq/kg of potassium per hour may be given intravenously, with careful ECG monitoring. The intravenous solution of potassium should be dilute enough to avoid local irritation; however, especially in infants, care must be taken to avoid intravenous fluid overload.

DOSAGE AND ADMINISTRATION

Recommended dosages are average values that may require considerable modification because of individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended doses.

Due to the more complete absorption of digoxin from soft capsules, recommended oral doses are only 80% of those for tablets, elixir, and IM injection.

Because the significance of the higher peak serum concentrations associated with once-daily capsules is not established, divided daily dosing is presently recommended for:

1. infants and children under 10 years of age;
2. patients requiring a daily dose of 300 μg (0.3 mg) or greater;
3. patients with a previous history of digitalis toxicity;
4. patients considered likely to become toxic;
5. patients in whom compliance is not a problem.

Where compliance is considered a problem, once-daily dosing may be appropriate.

Adults:

Adults: rapid digitalization with a loading dose—Peak body digoxin stores of 8 to 12 μg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Larger stores (10 to 15 μg/kg) are often required for adequate control of ventricular rate in patients with atrial flutter or fibrillation. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (i.e., 6 to 10 μg/kg [see PRECAUTIONS section]).

The loading dose should be based on the projected peak body stores and administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6- to 8-hour intervals, *with careful assessment of clinical response before each additional dose.*

If the patient's clinical response necessitates a change from the calculated dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

Dosage for Previously Undigitalized Patients:

In previously undigitalized patients, a single initial Lanoxicaps dose of 400 to 600 μg (0.4 to 0.6 mg) usually produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2 to 6 hours. Additional doses of 100 to 300 μg (0.1 to 0.3 mg) may be given cautiously at 6- to 8-hour intervals until clinical evidence of an adequate effect is noted. The usual amount of Lanoxicaps that a 70-kg patient requires to achieve 8 to 15 μg/kg peak body stores is 600 to 1000 μg (0.6 to 1.0 mg).

Adults: gradual digitalization with a maintenance dose—The following table provides average Lanoxicaps daily maintenance dose requirements for patients with heart failure based upon lean body weight and renal function:

Usual Lanoxicaps Daily Maintenance Dose Requirements (μg) for Estimated Peak Body Stores of 10 μg/kg

Corrected Ccr (ml/min per 70 kg)	Lean body weight (kg/lbs) 50/110	60/132	70/154	80/176	90/198	100/220	Number of days before steady-state achieved
0	50	100	100	100	150	150	22
10	100	100	100	150	150	150	19
20	100	100	150	150	150	200	16
30	100	150	150	150	200	200	14
40	100	150	150	200	200	250	13
50	150	150	200	200	250	250	12
60	150	150	200	200	250	300	11
70	150	200	200	250	250	300	10
80	150	200	200	250	300	300	9
90	150	200	250	250	300	350	8
100	200	200	250	300	300	350	7

Example—Based on the above table, a patient in heart failure with an estimated lean body weight of 70 kg and a Ccr of 60 ml/min should be given 200 μg (0.2 mg) of Lanoxicaps per day, usually taken as a 100 μg (0.1 mg) capsule after the morning and evening meals. Steady-state serum concentrations should not be anticipated before 11 days.

Digitalizing Dose for Children:

Usual Digitalizing and Maintenance Dosages for Lanoxicaps in Children With Normal *Renal Function Based on Lean Body Weight*

Age	Digitalizing* Dose (μg/kg)	*Daily*† Maintenance Dose (μg/kg)
2-5 Years	25-35	25%-35% of the oral or IV loading dose‡
5-10 Years	15-30	
Over 10 Years		

*IV digitalizing doses are the same as Lanoxicaps digitalizing doses.

†Divided daily dosing is recommended for children under 10 years of age.

‡Projected or actual digitalizing dose providing desired clinical response.

More gradual digitalization can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided above can be used in calculating this dose for patients with normal renal function. In children with renal disease, digoxin dosing must be carefully titrated based upon desired clinical response.

Long-term use of digoxin is indicated in many children who have been digitalized for acute heart failure, unless the cause is transient. Children with severe congenital heart disease, even after surgery, may require digoxin for prolonged periods.

It cannot be overemphasized that both the adult and pediatric dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.

HOW SUPPLIED

LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 50 μg (0.05 mg): bottles of 100. Imprint A2C (red)

LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 100 μg (0.10 mg)†: bottles of 100. Imprint B2C (yellow)

LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 200 μg (0.20 mg)†: bottles of 100. Imprint C2C (green)

†U.S. Patent No. 4088750

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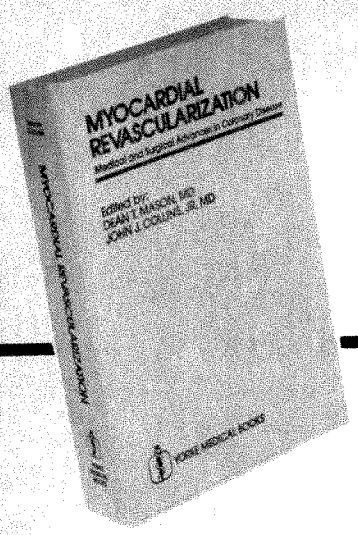

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Before prescribing, please consult current complete prescribing information, a summary of wh follows: **Indications:** For suppression and prevention of recurrence of the following cardiac ar rhythmias: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion). Norpace is equally effective in both digitalized and nondigitalized patients. I is also equally effective in treating primary cardiac arrhythmias and those which occur in asso ation with organic heart disease including coronary artery disease. Norpace CR should not be used initially if rapid establishment of disopyramide plasma levels is desired. Oral disopyramide phosphate has not been adequately studied in patients with acute myocardial infarction or with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patient with serious ventricular ectopic activity has not been established. **Contraindications:** Cardiogen shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug. **Warnings: Norpace or Norpace CR may cause or worsen congestive heart failure (CHF) or produce severe hypotension as a consequence of its negativ inotropic properties. Hypotension has been observed primarily with primary cardiomyopath or inadequately compensated CHF. Norpace or Norpace CR should not be used in patients with uncompensated or marginally compensated CHF or hypotension unless the condition secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace or Norpace CR, but careful attention must be given to maintaining cardiac function, including optimal digitalization. If hypotension occurs or CHF worsens, Norpace Norpace CR should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace or Norpace CR should be discontinued if significant widening (greater than 25%) of the QRS complex occurs. Pro longation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may b at particular risk. If Q-T prolongation greater than 25% is observed and if ectopy continues the patients should be monitored closely, and discontinuation of Norpace or Norpace CR considered. In rare instances significant hypoglycemia has been reported during Norpace therapy. The concomitant use of Norpace or Norpace CR with other Type 1 antiarrhythmic agents and/or propranolol should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. Patients receiving more than one antiarrhythmic drug must be carefully monitored. If first-degree heart block develops, the dosage of Norpace or Norpace CR should be reduced. If the block persists, continuation of Norpace or Norpace CR must depend upon an assessment of benefit versus risk. Development of second- or third-degree AV block or uni-, bi-, or trifascicular block requires discontinuation of drug unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic activity, disopyramide phosphate should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken. In patients with a family history of glaucoma, intraocular pressure should be measured before initiating Norpace or Norpace CR therapy. Precautions:** Patients with atrial flutter or fibrillation should be digitalized prior to Norpace or Norpace CR administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace or Norpace CR is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of disopyramide phosphate. Therefore, a loading dose of Norpace should not be given to such patients, and initial dosage and subsequent dosage adjustments should be made under close supervision. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs for overdosage. Norpace CR is not recommended for patients with severe renal insufficiency. Concomitant administration of disopyramide phosphate with phenytoin or other hepatic enzyme inducers may cause lower disopyramide plasma levels; whereas with quinidine, disopyramide levels may increase and quinidine levels may decrease. Antiarrhythmic drugs may be ineffective in patients with hypokalemia, and their toxic effects may be enhanced in patients with hyperkalemia. Therefore, potassium abnormalities should be corrected before starting Norpace or Norpace CR therapy. Safe use in pregnancy has not been established. Disopyramide has been found in human fetal blood. **Norpace has been reported to stimulate contractions of the pregnant uterus.** Use of Norpace or Norpace CR in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. Following oral administration, disopyramide has been found in human milk at a concentration not exceeding that in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted. Effects of Norpace or Norpace CR on the fetus during delivery or on the course of labor and delivery are unknown. **Adverse Reactions:** Dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention, urinary frequency and urgency, impotence, nausea, pain/bloating/gas, anorexia, diarrhea, vomiting, nervousness, dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains, hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain, generalized rash/dermatoses, itching, hypokalemia, elevated cholesterol/triglycerides, depression, insomnia, dysuria, numbness/tingling, elevated liver enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, and hypoglycemia. Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported, as have fever, respiratory difficulty, thrombocytopenia, and gynecomastia. **Dosage and Administration:** Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg/day given in divided doses: q6h for Norpace and q12h for Norpace CR. **See current complete prescribing information for dosage recommendations.**

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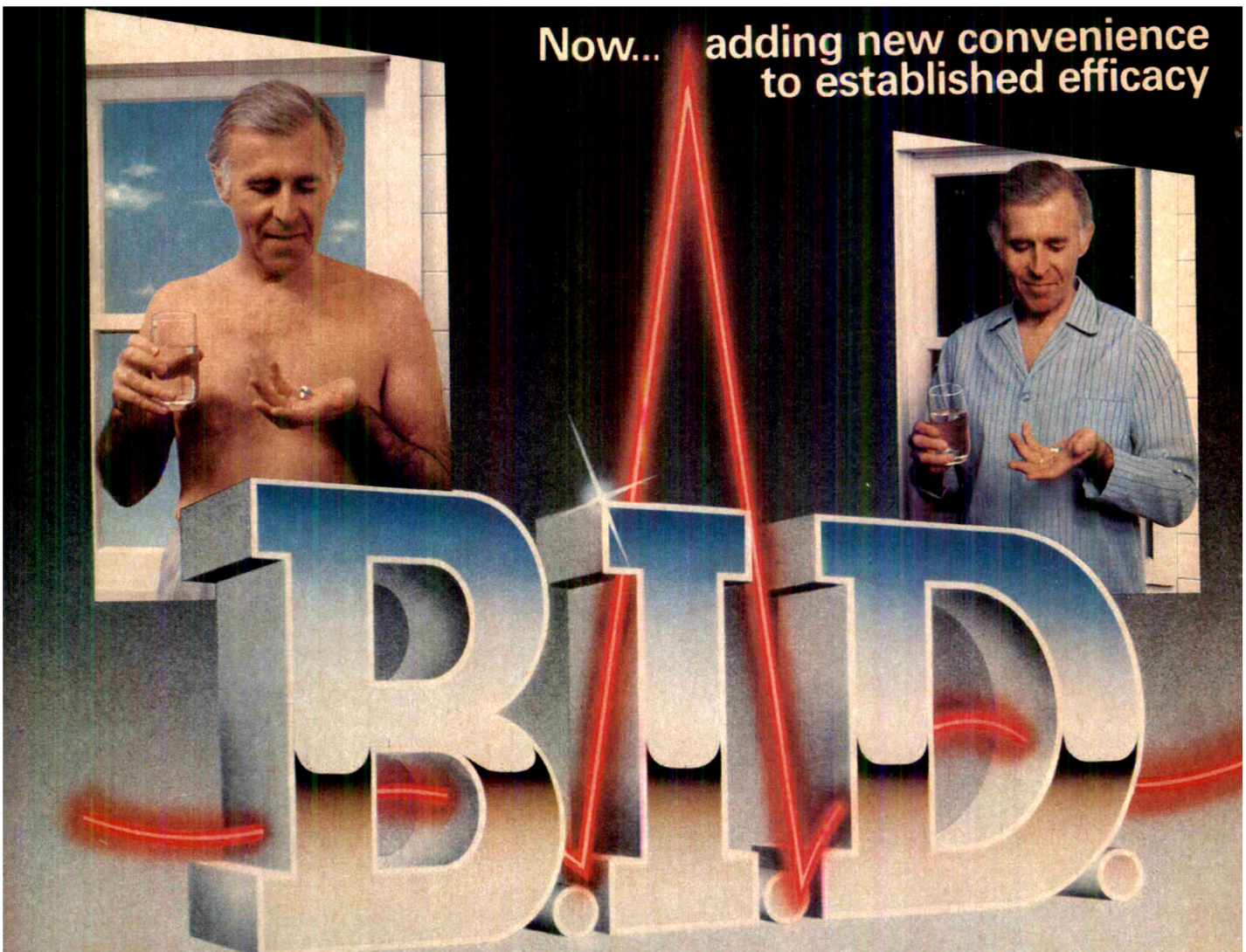

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SEARLE

Improved Radiation Protection for Physicians Performing Cardiac Catheterization

EDWARD W. GERTZ, MD, JUDITH A. WISNESKI, MD, ROBERT G. GOULD, ScD, and JOHN R. AKIN, MD

Physicians and their assistants performing diagnostic angiography must be concerned with the radiation exposure they receive. The introduction of hemiaxial projections for imaging has increased diagnostic accuracy but has also greatly increased the physicians' exposure to scattered radiation. This increase is especially critical for the eyes and thyroid of the physician who routinely performs these procedures. To reduce such exposure a ceiling-suspended shield (60 × 45 cm), made of 6.4 mm glass with a 19.5 kg/m^2 (4 lb/ft^2) lead equivalency, was developed. During procedures the shield is interposed between the physician and the region of the patient acting as the source of scattered radiation. The degree of radiation protection to the operator was assessed by measuring the distribution of scattered radiation in the vicinity of the operator with and without the shield. The effectiveness of the shield was determined in the 30° right anterior oblique (RAO), 5° left anterior oblique (LAO), 35° LAO, and 50° LAO-15° cranial angulations. At critical heights such as the level of the eyes and thyroid, scattered radiation levels were reduced by 85% or greater in all angulations. Without interfering with the physician's ability to observe the patient or manipulate the catheter, this shield can significantly reduce the physician's exposure to radiation.

Several investigations have measured radiation exposure to the physician during cardiac catheterization and coronary angiography.[1-7] Most of these investigations were performed using a fixed undertable x-ray tube or a U-arm system. The exposure levels reported in these studies are excessive for physicians who perform angiography routinely. Guidelines have been established for occupational radiation exposure.[8] Because of exposure to critical organs such as the eyes and thyroid, compliance with these guidelines may require that the physician perform only several procedures a week.[1,2]

Radiographic systems with high output capacity generators and x-ray tubes have recently been introduced, thus providing the potential for better definition of vessels and lesions on cineangiography. In addition, C-arm and parallelogram support structures are being used which allow the physician to easily obtain hemiaxial views. These developments enhance the diagnostic accuracy of coronary angiography[9-11]; however, the radiation exposure to the operator is potentially greater with these systems than with older undertable-mounted x-ray tube systems.

To reduce the physician's radiation exposure, a protective shield was developed in the cardiac catheterization laboratory at the San Francisco Veterans Administration Medical Center. The purpose of this study was to assess the effectiveness of this shield in reducing the radiation exposure to the physician performing cardiac catheterization with a poly C-arm system.

Methods

The radiographic equipment consists of a Poly Diagnost C System and a Maximus M-100 Generator (Philips Medical Systems). The Poly Diagnost C has a U-arm type imaging system with a parallelogram support. In addition to the left-right rotation of the x-ray tube and intensifier, the parallelogram support allows isocentric cranial and caudal angulation.

The radiation protection shield (Fig. 1) is made of transparent 6.4 mm glass (60 × 45 cm) with a 19.5 kg/m^2 (4 lb/ft^2) lead equivalency. Attached to the bottom of the glass is a piece of flexible leaded rubber 22 cm long with 19.5 kg/m^2 lead equivalency.

From the Departments of Medicine and Radiology and the Cardiovascular Research Institute, University of California, San Francisco, and the Veterans Administration Medical Center, San Francisco, California. This work was supported by the Medical Research Service of the Veterans Administration, San Francisco, California. Manuscript received May 11, 1982, accepted June 8, 1982.

Address for reprints: Edward W. Gertz, MD, Veterans Administration Medical Center (111C1), 4150 Clement Street, San Francisco, California 94121.

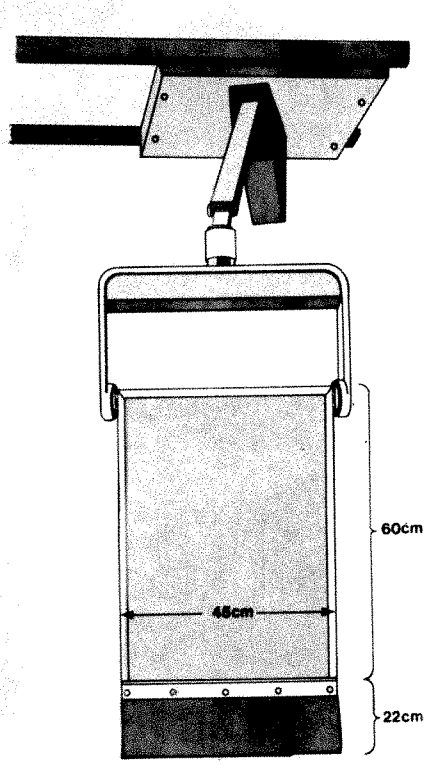

FIGURE 1. Diagram of the radiation protection shield with ceiling mount.

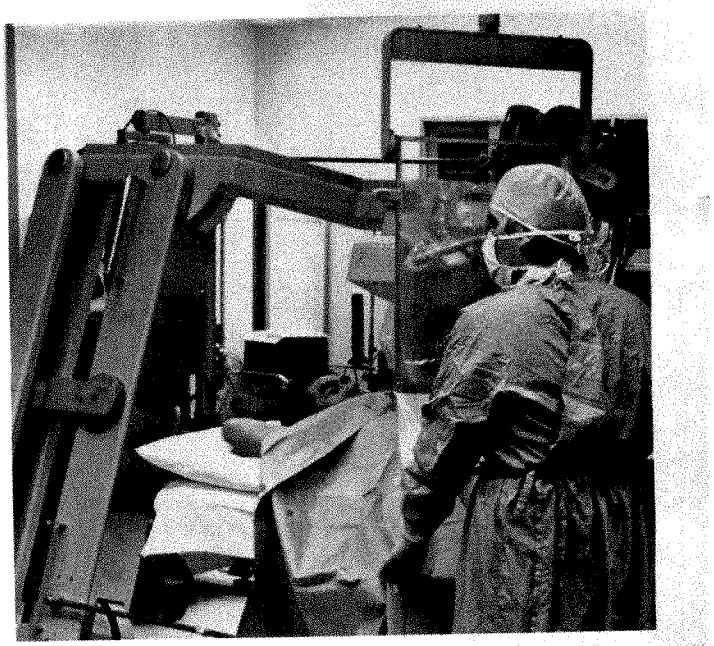

FIGURE 2. Photograph illustrating the use of the shield during cardiac catheterizations performed through the femoral approach.

The shield is mounted on ceiling rails with a swivel arm allowing for easy mobility in the longitudinal and vertical planes. In addition, it is counterbalanced to allow for easy vertical movement. During procedures the shield is draped with a sterile, transparent cover. Therefore, the physician performing the procedure can position the shield between himself and the x-ray scattering source (patient and x-ray tube) (Fig. 2). The flexible leaded rubber attached to the bottom of the glass is designed to lie on the patient, thus providing additional protection by eliminating the scattered radiation which would reach the operator beneath the leaded glass.

The radiation protection afforded by the shield was determined by measurements of radiation levels in the vicinity of the operator with and without the shield in place. A Rando anthropomorphic phantom was used in this study. This whole body phantom contains human bones and is comprised of materials which simulate human soft tissue. Its shape is that of an adult male weighing 70 kg with a 22 cm chest diameter. The radiation levels were measured with a Victoreen Panoramic survey meter during fluoroscopy at 95 kVp and 1 mA. The effectiveness of the shield was determined with the x-ray tube aligned in the following projections: 30° RAO, 5° LAO, 35° LAO, and 50° LAO-15° cranial angulation.

Results

Table I gives a comparison of radiation exposure levels for the various anatomic locations of the operator without and with the shield. The values listed are for an operator who is 5 feet, 10 inches tall and standing in the position shown in Figure 2 with the height of the catheterization table at 90 cm. These radiation levels were obtained with the phantom simulating the patient. As shown in Table I, there is a significant reduction in radiation exposure afforded by the shield to all anatomic areas above and including the pelvis. For the eyes and thyroid, which are of critical concern, there was an 85% or greater reduction in exposure levels for all angulations.

To further illustrate the effectiveness of this shield, the isoexposure curves for the 50° LAO-15° cranial angulation are shown in Figure 3. This angulation is commonly used during cardiac cineangiography to better visualize the left main coronary artery, the proximal left anterior descending artery, and the distal right coronary artery. Using this cranial angulation, the eyes and thyroid of the operator are exposed to 41 mR/h during fluoroscopy at 95 kVp and 1 mA. For a 10 second cineangiogram at 30 frames/s and 2.8 mAs/frame, the exposure to the eyes and thyroid of the operator would be 9.6 mR. For an identical angiogram with the x-ray tube in the same projection, use of the protective shield would reduce the exposure to these organs to 0.2 mR.

It should be noted that the effectiveness of the shield does not significantly depend on the x-ray tube potential. The equivalent lead thickness of this shield is 1.58 mm. Thus, even for x-rays of 150 kV, less than 3% will penetrate the glass.

Discussion

Concern has been expressed over the radiation exposure to physicians performing cardiac catheterizations. Previous studies have documented that the physician performing catheterization and his assistant can receive significant radiation exposure.[1–7] The irradiation of the physician primarily results from scattered radiation arising within the patient from the tissues penetrated by the primary beam. The exposure received during 1 second of fluoroscopy is approximately equal to that received during 1 cineangiographic frame. Thus,

TABLE I Radiation Exposure Levels (milliroentgen/hour)

Anatomic Location	X-Ray Tube Angulation			
	30° RAO: Without/With Shield	5° LAO: Without/With Shield	35° LAO: Without/With Shield	50° LAO-15° Cranial: Without/With Shield
Eyes, thyroid	3.8/0.5	12/0.6	25.5/0.5	41/0.7
Chest	6.5/0.7	18.5/0.8	33/0.7	58/0.7
Pelvis	10/1.4	18.5/5.9	27/5.7	57/3.2
Lower legs	38/36	31/31	45/45	2.5/1.8

during a cardiac catheterization, 50 to 80% of the physician's exposure occurs during cineangiography.[1,2] The actual exposure level will vary depending on the radiographic equipment and the type of procedure involved. With the advent of C-arm and parallelogram-supported imaging systems to obtain the hemiaxial views, exposure levels to the physician can be increased; greater emphasis should be placed on the radiation protection of physicians routinely performing cardiac catheterizations.

This study measured the radiation exposure levels for physicians using a Philips Poly Diagnost C System in 4 different angulations. As shown in Table I, the LAO-cranial angulation has the greatest potential for exposure to the physician's chest, eyes, and thyroid. The thyroid and the lens of the eye, which are not shielded by the routine lead apron, remain the most critical organs for radiation exposure for individuals routinely performing catheterization. Radiation-induced cataracts are well described in animals and humans who are chronically exposed to ionizing radiation; the dose-response curve appears to have a threshold.[12] There is a higher incidence of thyroid carcinoma in persons exposed to both therapeutic and occupational radiation; this probably follows a linear dose-response curve.[12] The maximal exposure recommended is 5 R/year (100 mR/wk) for the lens of the eye and 15 R/year (300 mR/week) for the thyroid.[8]

Protection devices are available for individual organs: thyroid shields and leaded eyeglasses. However, eyeglasses are only effective in protecting the lens of the eye from scattered radiation when the operator is looking in the direction of the source of radiation, that is, looking directly at the part of the patient that is being irradiated. Generally the physician is watching the television monitor during fluoroscopy or cineangiography. Thus, the eyeglasses may not be effective in reducing exposure to this organ. The shield described in this report protects these individual organs while decreasing the general exposure to the pelvis, chest, and face.

In addition to the protective devices for the individual organs, other shields or screens have been designed to decrease the operator's exposure.[2,3,13] In order to be of value, the device or shield must exhibit the following features: (1) it must be effective in reducing the scattered radiation to the operator in the various projections; (2) it must not interfere with patient care and catheter manipulation; and (3) it must be easy and comfortable for the operator to use. The protective

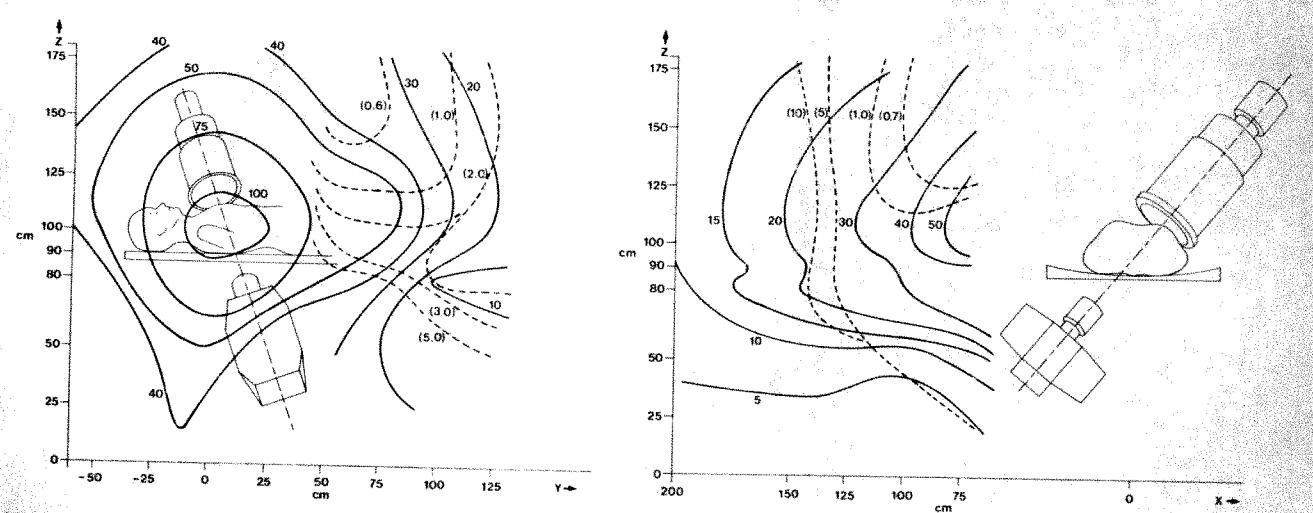

FIGURE 3. Isoexposure curves expressed in milliroentgen/hour for the 50° LAO-15° cranial angulation in (**left**) the longitudinal plane with the operator at 75 cm on the Y axis, and (**right**) the horizontal plane with the operator at 75 cm on the X axis. The **solid lines** give the radiation exposure levels *without* the protection of the shield; the **dashed lines** show the values *with* the shield. The vertical center of shield is at 75 cm in both the X and Y planes with the operator behind the shield as shown in Figure 2. Z represents the vertical plane, Y the longitudinal plane, and X the horizontal plane.

shield described in this report meets these criteria. This shield reduces the physician's exposure to the eyes and thyroid by at least 85% in all views (Table I). For example, during fluoroscopy at 95 kVp and 1 mA in the LAO-cranial angulation, it reduces the exposure level from 41 to 0.7 mR/hour. This shield is thus effective in reducing the scattered radiation to the thyroid and the eyes of physicians performing cardiac catheterization.

Our shield also has the second and third features described above. It is made of transparent glass and covered with a transparent, sterile cover during the procedure; thus, the physician is able to observe the patient. With the mobility afforded by the ceiling rails, swivel arm, and counterbalance, the physician can easily position the shield before fluoroscopy and cineangiography. The shield is positioned with the flexible leaded rubber on the patient's lower abdomen, so it does not interfere with catheter manipulation at the groin site. This shield has been in daily use for over 2.5 years in the cardiac catheterization laboratory at the San Francisco Veterans Administration Medical Center.

This study assesses the potential radiation exposure to physicians performing cardiac catheterization using a Poly C Diagnost System. The radiation exposure to the eyes and thyroid is considerably increased using the LAO-cranial view compared with the traditional RAO and LAO views. A leaded glass shield is described which was found to be effective in significantly reducing (>85%) the physician's radiation exposure in all angulations. In addition, this shield does not interfere with patient observation or catheter manipulation.

Acknowledgment: We express our appreciation to Helen Smeeton for her secretarial assistance and to Lee Pickens and Albert Koetsier of the Philips Medical Systems for photography.

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Compression of the Superior Vena Cava and Right Atrium In Cardiac Tamponade

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In an attempt to identify specific angiographic patterns which might be useful in distinguishing cardiac tamponade from constrictive pericarditis and other causes of right atrial hypertension, we studied the angiographic and hemodynamic characteristics of 10 patients with cardiac tamponade and compared these with similar characteristics in a comparable group of patients with either constrictive pericarditis, effusive-constrictive pericarditis, or pericardial effusion with left ventricular failure. Two predictive angiographic patterns of cardiac tamponade were noted: (1) a tapering or local lateral indentation of the intrapericardial portion of the superior vena cava, and (2) an exaggerated phasic variation in the diameter of the superior vena cava at its junction with the right atrium. Using the ratio of the minimum-to-maximum diameter of the intrapericardial superior vena cava (caval compression ratio), a stepwise logistic regression indicated that when this ratio was <0.62, cardiac tamponade was present with a sensitivity of 80%, a specificity of 90%, and a p value <0.001. The change in diameter of the superior vena cava between systole and diastole (phasic narrowing ratio) also was a discriminator of cardiac tamponade (p <0.04). Two-dimensional echocardiographic studies in an additional group of 10 patients with cardiac tamponade demonstrated marked concavity of the right atrial free wall, which corresponded temporally to the angiographic abnormality, but was even more marked than that noted on the cineangiograms. These results indicate that specific changes can be appreciated on superior vena cavography and can be useful in distinguishing cardiac tamponade from other pericardial or myocardial processes associated with right atrial hypertension.

Compression of the heart by fluid within the pericardium—cardiac tamponade—can produce major changes in the shape,[1-4] size,[1,5-11] and motion[1,6,10-14] of the 4 cardiac chambers and thereby significantly impair cardiac function. The severity of these alterations is influenced by the amount of fluid within the pericardium, the underlying disease process, and the location or loculation of the fluid. When tamponade is clinically suspected and a diagnosis cannot be made noninvasively, right heart catheterization is usually indicated for hemodynamic measurements. In addition, right atrial angiography may provide morphologic information to help establish the diagnosis.[15] Hemodynamically, tamponade is characterized by a decreased cardiac output, equalization of atrial mean and ventricular end diastolic pressures, and an absent *y* descent in the right atrial pressure tracing.[16-19] Right atrial angiography demonstrates an increased separation between the right atrial cavity and the lung, small cardiac chambers, prolonged circulation time through the heart, inferior vena caval reflux, and straightening of the lateral wall of the right atrium.[2-4,6] Unfortunately, none of these angiographic signs is specific for tamponade and similar findings may be present when there is constrictive pericarditis with pericardial thickening. Some of these findings may be present with restrictive cardiomyopathy.[3,20-23]

In order to determine whether other specific angiographic signs of tamponade exist, the angiograms of a series of patients with proven cardiac tamponade were compared with those of other patients with pericardial diseases but without hemodynamic evidence of tamponade.

Methods

Twenty patients who underwent cardiac catheterization and angiography for possible pericardial heart disease were classified on the basis of hemodynamic parameters into a group with cardiac tamponade (Group 1) and a control group with other pericardial diseases (Group 2). The age range and sex ratio were similar in both groups (Table I). The criteria for cardiac tamponade included (1) a diminutive or absent *y*

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TABLE 1 Clinical and Hemodynamic Data*

	Age (yr) & Sex	RA	RV	PA	PCW
			Group 1: Patients With Tamponade		
1	62M	13	25/12	25/5	...
2	74M	16	28/14	28/14	17
3	41F	13	30/14	30/18	15
4	70M	18	35/16	35/17	18
5	40F	16	38/15	35/20	19
6	74M	15	40/18	40/20	20
7	44M	13	40/10	40/8	...
8	65F	19	35/21	35/21	21
9	47F	10	32/15	32/15	...
10	58F	11	40/13	40/11	12
			Group 2: Control Patients		
1	39M	5	30/10	30/12	14
2	54F	20	60/18	60/25	29
3	52M	18	36/19	37/20	21
4	50M	13	30/12	30/10	12
5	73F	14	38/17	38/17	17
6	67F	12	50/15	50/15	15
7	57M	15	40/15	40/16	18
8	23M	23	40/23	40/22	22
9	61M	6	27/13	27/14	5
10	55F	7	32/7	22/8	9

* All pressures in mm Hg. PA = pulmonary artery systolic and diastolic pressure; PCW = mean pulmonary capillary wedge pressure; RA = mean right atrial pressure; RV = right ventricular systolic and diastolic pressure.

descent in the right atrial pressure tracing, (2) equalization within 4 mm Hg of the mean right atrial, right ventricular end-diastolic, pulmonary arterial diastolic, and mean pulmonary capillary wedge pressures, and (3) the withdrawal of a significant amount of fluid during pericardiocentesis with clinical and hemodynamic improvement.

The control group had other types of pericardial heart disease. Seven patients had pericardial constriction with a prominent *y* descent and a "dip and plateau" configuration of the ventricular diastolic pressure tracing. Three patients had pericardial effusion without tamponade but with left ventricular failure. Mean right atrial pressure in Group 1 was 14 ± 3 mm Hg (mean ± standard deviation) and in Group 2 was 13 ± 6 mm Hg. Mean pulmonary capillary wedge pressure in Group 1 was 14 ± 4 mm Hg and in Group 2 was 16 ± 7 mm Hg. Neither mean right atrial nor pulmonary capillary wedge pressure was statistically different in Groups 1 and 2. One patient from Group 1 and 4 patients from Group 2 had had previous heart surgery.

Superior vena caval cineangiography was performed in the posteroanterior projection, with the catheter placed in the superior vena cava between the azygos vein and the right atrium. Contrast material was injected at a rate of 20 ml per second for 2 seconds. Filming included the superior vena cava between the azygos vein and the heart, the right atrial cavity and its wall so that the right lung could be seen, the proximal 1 to 3 cm of the inferior vena cava, and delayed visualization of the remainder of the heart. The angiograms were interpreted independently of the hemodynamic measurements.

The superior vena cava was analyzed as shown in Figure 1. Two kinds of measurement were made. The caval compression ratio was defined as the minimum diameter (c) of the right atrial-superior vena caval junction during the cardiac cycle divided by the maximum diameter (a) of the superior vena cava, which usually occurred just below the azygos vein. The phasic change in caval diameter (phasic narrowing ratio) was measured at the right atrial-superior vena caval junction and was the ratio of the minimum (c) to maximum (b) width during the cardiac cycle. The shape of the lateral right atrial cavity was graded as convex, straight, or concave. Reflux was said to occur into the inferior vena cava if at least 1 cm was opacified.

Statistical analysis consisted of the computation of a probability model for discriminating the tamponade group from the nontamponade group on the basis of predictor (angiographic) measurements. This was done by means of the BMDP program for stepwise logistic regression, BMDPLR.[24] Sensitivity and specificity of this resulting probability model were also estimated by the program. Comparison of mean predictors in the 2 groups was performed by Student's *t* test.

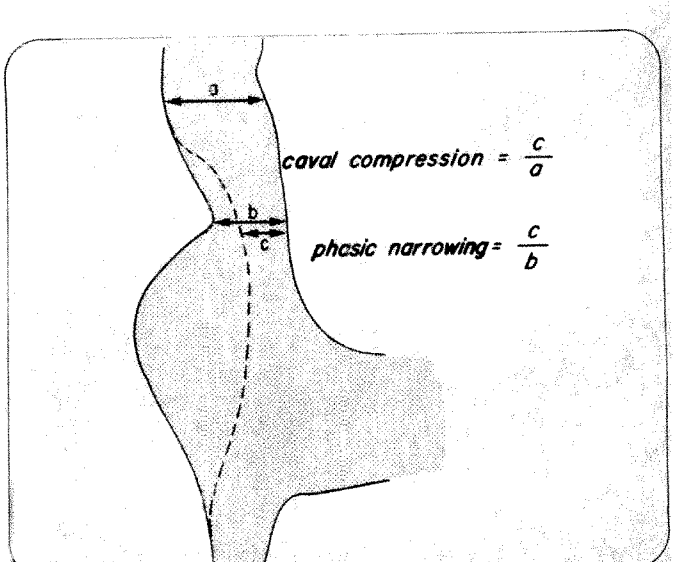

FIGURE 1. Line drawing of a superior vena caval and right atrial angiogram illustrating measurement of the caval compression and phasic narrowing ratios. The **dotted line** represents the right atrial free wall in systole.

An additional group of 10 patients with cardiac tamponade was studied by 2-dimensional echocardiography. Tamponade was defined by the same hemodynamic criteria as were used in the angiographic groups. The intrapericardial pressures were elevated, with a mean of 17 mm Hg and a range of 9 to 31 mm Hg. All patients showed hemodynamic improvement after pericardiocentesis. This group included 4 females and 6 males, with a mean age of 48 years (range 16 to 76). In each of these cases, the right atrial free wall was recorded using the conventional parasternal short-axis, apical 4 chamber, and subcostal views, and its configuration and phasic motion were examined.[25]

Results

Changes in the superior vena cava: The intrapericardial portion of the superior vena cava was distorted in all patients with cardiac tamponade. A typical superior vena caval angiogram (Fig. 2) demonstrated a long, tapered narrowing inferior to the azygos vein termination, extending inferiorly to the right atrium. The configuration of the superior vena cava varied from a symmetrical tapering to a sharply demarcated defect in its lateral wall below the right pulmonary artery (Fig. 3A) or a combination of this defect with concavity and medial displacement of the cava (Fig. 3B).

In addition to these changes in the configuration of the superior vena cava, there was an exaggerated variation in caval diameter which changed with the cardiac cycle. Cineangiograms taken during tamponade characteristically demonstrated increased narrowing of the intrapericardial superior vena cava throughout atrial systole (Fig. 4). The extent of this phasic narrowing varied; in 1 case the lumen of the cava measured 5 mm after correction for magnification. In contrast, the caval angiograms in patients with pericardial effusion without tamponade (Fig. 5A) and pericardial constriction (Fig. 5B) showed a convex or straight lateral border to the superior vena cava and right atrium.

The change in diameter of the superior vena cava from its minimal width at the right atrial junction to its maximal width below the azygos vein (caval compression ratio) ranged from 0.23 to 0.79 in Group 1 with tamponade and from 0.53 to 0.88 in Group 2 (Table II). The mean caval compression ratio (0.5 ± 0.05 standard error of the mean [SEM]) in the tamponade group differed significantly by Student's t test from that in the nontamponade group (0.74 ± 0.04 [SEM], $p = 0.001$).

The phasic narrowing ratio of the superior vena cava, measured only at the superior vena cava-right atrial junction, ranged from 0.34 to 0.85 for the tamponade group, and from 0.64 to 0.91 for the control group. The

FIGURE 2. Typical superior vena cavogram in cardiac tamponade demonstrating a gradual lateral concavity of the superior vena cava below the right pulmonary artery. Additional abnormalities include the flat shape of the free wall of the right atrium, inferior vena caval reflux, filling of the azygos vein (**arrow**), concavity of the anteroseptal wall of the right ventricle, superior displacement of the heart above the diaphragm, and increased separation of the lung from the right atrial cavity. Caval compression ratio = 0.52.

FIGURE 3. Variations in the shape of the superior vena cava during atrial systole in tamponade. **Left,** the superior vena cava (**arrows**) has a lateral step near the right atrial junction. Extrinsic compression is indicated by the small right atrial size, tricuspid stenosis, inferior vena caval reflux, and increased separation of the lung from the atrial cavity. Caval compression ratio = 0.46; phasic narrowing ratio = 0.73. **Right,** medial displacement of the superior vena cava (**arrows**) with a lateral step in atrial systole indicates tamponade, along with the less specific inferior vena caval reflux. The anteroseptal right ventricular wall is abnormally concave, compressed anteriorly by fluid. Caval compression ratio = 0.39; phasic narrowing ratio = 0.54.

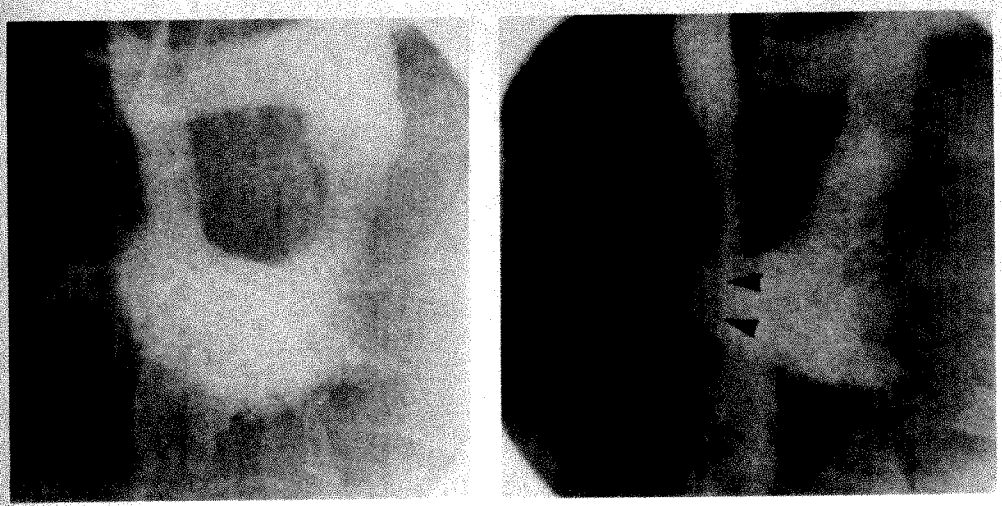

FIGURE 4. Dynamic change in the shape of the superior vena cava during **(left)** atrial diastole and **(right)** atrial systole in cardiac tamponade. The anterolateral wall of the right atrium remains convex **(arrow)** while the posterior wall segment is concave **(arrowheads)**.

mean phasic narrowing ratio also differed between the 2 groups, 0.66 ± 0.05 for tamponade versus 0.8 ± 0.04 (SEM) in the nontamponade group, $p < 0.04$.

Stepwise logistic regression revealed that the caval compression ratio was superior ($F = 15$) as a discriminator to the phasic narrowing ratio ($F = 5$). In fact, the final probability model produced by stepwise logistic regression rejected both the phasic narrowing ratio and the right atrial wall shape as not containing any significant additional discriminating power beyond that of the caval compression ratio. Using a cutpoint in predicted probability of tamponade versus other pericardial diseases of $p > 0.62$ (that is, predicted probability of tamponade >0.62 was judged a diagnosis of tamponade), the probability model which emerged from the logistic regression using the caval compression ratio had a sensitivity of 80% and a specificity of 90%.

Other radiologic signs of pericardial disease: Other radiologic signs of pericardial disease were present but not specific. In 9 of 10 patients in both Groups 1 and 2, reflux occurred down the inferior vena cava and frequently into the hepatic veins. This sign presumably reflects the high right atrial pressure. The right atrial wall in those patients with tamponade was concave in 7, straight in 1, and convex in 2. In the control group, the shape of the lateral right atrial wall was concave in 9 and straight in 1. An increased distance between the right atrial cavity and the right lung was present in all with tamponade and varied markedly in those in Group 2.

Similar abnormal changes in the configuration of the right atrial free wall were noted on 2-dimensional echocardiography. All 10 patients with tamponade had marked concavity of the right atrial free wall during atrial relaxation and ventricular isovolumic systole (Fig. 6). During subsequent atrial filling and ventricular ejection, the right atrial free wall resumed a normal convex configuration. In 3 patients 2-dimensional echocardiography was performed after pericardiocentesis. These studies demonstrated that the right atrial free wall resumed a normal configuration and was no longer inverted at any point during the cardiac cycle.

Discussion

This study suggests that the shape of the proximal superior vena cava can reliably distinguish cardiac tamponade from other pericardial diseases associated with abnormal right atrial hemodynamic function. This distinction could be made even though elevated right atrial pressures were present in both the group with tamponade (14 ± 3 mm Hg) and the control group (13 ± 6 mm Hg). Since all but 1 of our patients had a mean right atrial pressure of at least 10 mm Hg, these angiographic signs may not be present in patients with low pressure cardiac tamponade which can develop in the presence of hypovolemia. In the patient reported by

TABLE II Measurements of Superior Vena Caval Changes, Right Atrial Shape, and Inferior Vena Caval Reflux

	Caval Compression Ratio	Phasic Narrowing Ratio	Right Atrial Wall*	Inferior Vena Caval Reflux
Group 1: Patients With Tamponade				
1	0.50	0.23	1	Yes
2	0.73	0.46	1	Yes
3	0.50	0.45	1	Yes
4	0.34	0.32	1	Yes
5	0.79	0.79	−1	Yes
6	0.75	0.82	1	Uncertain
7	0.72	0.53	0	Yes
8	0.85	0.59	1	Yes
9	0.64	0.45	−1	Yes
10	0.80	0.64	1	Yes
Group 2: Control Patients				
1	0.59	0.53	1	Yes
2	0.91	0.85	1	Yes
3	0.85	0.75	1	Yes
4	0.72	0.65	1	Yes
5	0.90	0.73	0	Yes
6	0.64	0.64	1	No
7	0.88	0.88	1	Yes
8	0.79	0.76	1	Yes
9	0.86	0.77	1	Yes
10	0.89	0.82	1	Yes

* Convex = 1; concave = −1; straight = 0.

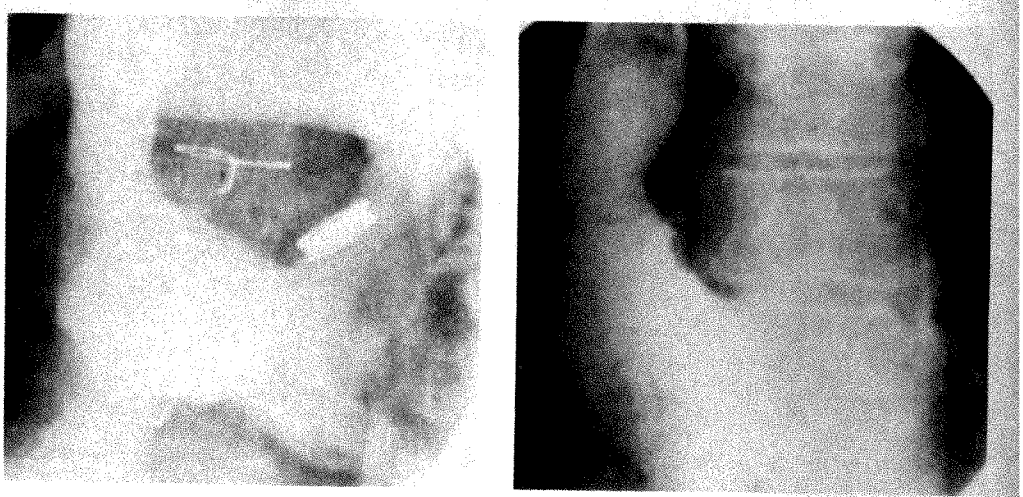

FIGURE 5. Superior vena caval angiograms in 2 patients whose right heart hemodynamic function indicated constriction. **Left,** straight free wall of the right atrium, inferior vena caval reflux, and decreased filling of the right ventricle. Caval compression ratio = 0.73; phasic narrowing ratio = 0.90. **Right,** slightly convex lateral wall of the cava and right atrium. Caval compression ratio = 0.75; phasic narrowing ratio = 0.86.

Antman et al,[26] low pressure cardiac tamponade was present with a mean right heart pressure of 8 mm Hg. The mean right atrial pressure of 13 mm Hg in our series almost certainly precluded dehydration.

The superior vena caval shape and the phasic narrowing ratio predict the presence of tamponade even when other types of pericardial disease are present. When pericardial effusion coexists with thickening of the visceral and parietal pericardium, clinical and hemodynamic signs may be confusing because varying degrees of tamponade or constriction, or both, may be present.[27] The difficulty in distinguishing the various pericardial entities appears to result from a lack of specificity in the usual hemodynamic[1,9,15,19,28] and angiographic[2,3,4,20,22,23] signs, along with the frequent coexistence of both (effusive-constrictive pericarditis). In contrast to these previous studies, the caval compression ratio of the superior vena cava has a sensitivity of 80% and a specificity of 90% when the ratio is 0.62 or less. The caval compression ratio achieved this degree of differentiation between patients with and without tamponade even though the control group was biased against this distinction because all but 3 patients in the control group had right atrial pressure greater than 10 mm Hg. Using the probability model developed by the stepwise logistic regression analysis, we identified those patients who would not have been correctly classified by a caval compression ratio of 0.62 or less (Table II). There were 2 false-negative diagnoses in Group 1 and 1 false-positive diagnosis in Group 2. All 3 of these patients had effusive-constrictive pericarditis with right atrial pressure not falling to normal values after pericardiocentesis.

Several factors could influence the shape of the right atrium and superior vena cava when tamponade is present: the amount and location of the pericardial fluid, the size of the heart, the phase of respiration and of the cardiac cycle, and the presence of any loculated fluid or adhesions.[6,14] The volume of this fluid increases in the inferior regions with inspiration as the diaphragm descends. The cardiac cycle itself causes a redistribution of fluid with more fluid collecting anteriorly and to the left in ventricular systole and laterally to the right in ventricular diastole. The change in the distribution of

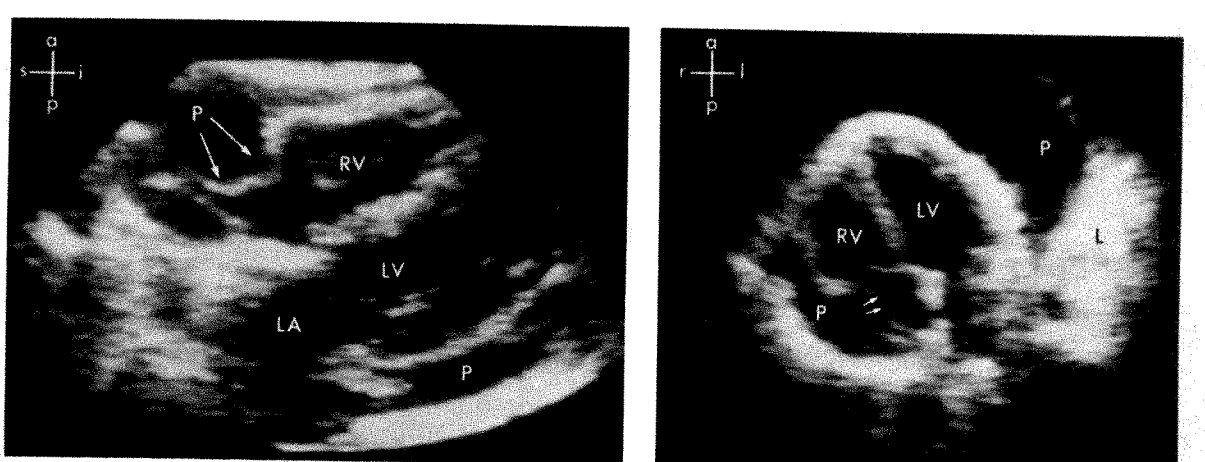

FIGURE 6. Left, 2-dimensional echocardiographic subcostal view of right atrial buckling (**arrows**) in cardiac tamponade. **Right,** apical 4-chamber view in a patient with lymphoma (L). The free wall of the right atrium is concave (**arrows**). a = anterior; l = left side; LV = left ventricle; P = pericardial fluid; p = posterior; r = right side; RV = right ventricle; LA = left atrium; s = superior; i = inferior.

pericardial fluid with the cardiac cycle offers an explanation of the concave or straight right atrial lateral border. This angiographic sign in our series usually was present in atrial systole but was quite variable in atrial diastole. A possible explanation is that the expansion of the right ventricle in diastole created a hydraulic increase in pressure, causing the right atrium to collapse its lateral wall inward. This mechanism is supported by our echocardiographic studies in patients with tamponade which demonstrate total reversal of the normal direction of curvature of the right atrial free wall after atrial systole. Since this type of motion cannot result from active muscular contraction, it must be caused by passive compression from without. Its temporal relation to maximal ventricular filling further suggests that the increased intrapericardial pressure expansion of one area of the heart must be accompanied by hydrodynamic compression of another area. Since the atria at end-atrial systole and early atrial diastole are the lowest pressure areas within the heart, it is to be expected that they would be most susceptible to deformity. The left atrium does not have a pericardial space adjacent to it, leaving the right atrium to suffer the greatest effects of this external compression.

The shape of the right atrial free wall in tamponade, as seen on the 2-dimensional echocardiogram, offers an explanation for the lack of sensitivity of the radiographic right atriogram. With angiography, the lateral wall of the right atrium may be convex, straight, or concave in the posteranterior projection when tamponade is present. In our 10 patients with tamponade who had echocardiograms, the right atrial wall was sharply concave and at times U-shaped. A portion of the right atrial wall always projected within the silhouette that would be cast by a radiographic study. The contrast medium in the lateral aspect of the right atrium then would obscure the medial invagination of the free wall. In Figure 4 the anterior right atrial wall is convex, while the posterior segment is concave, reflecting the buckle. If the right atrium were densely opacified, this posterior line would not be seen.

Various angiographic signs have been recognized for both effusive-constrictive and pure constrictive pericarditis.[3,4,20–23] Straightening of the right atrial contour and an increased width of the pericardium adjacent to the right atrium are present in most patients with pericardial disease. The lack of volume change during the last half of diastole in both ventricles is a hallmark of constrictive pericarditis, but this sign is usually absent when tachycardia is present. Angiographic analysis of left ventricular volume changes in patients with constrictive pericarditis have shown a faster than normal volume increase in early diastole.[28]

Since angiography entails a small but definite risk, the indications of superior vena cavography when tamponade is suspected must be tempered by the clinical situation, the expected gain in information, and the therapeutic options. When tamponade is obvious clinically and is confirmed by echocardiography, we perform pericardiocentesis without angiography. When the type of pericardial heart disease is not apparent after clinical examination and right heart catheterization, we utilize the configuration and motion of the superior vena cava and right atrium to differentiate patients whose dominant abnormality is cardiac tamponade from those who have other types of pericardial disease. Our preliminary observation on 2-dimensional echocardiography of buckling of the right atrial wall, along with the previous recognition of fluid loculation and intrapericardial abnormalities,[29] may allow noninvasive correlation with specific pericardial findings in the future.

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Occlusive Thromboaortopathy (Takayasu's Disease) And Pregnancy

Clinical Course and Management of 33 Pregnancies and Deliveries

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Twenty-seven Japanese patients with occlusive thromboaortopathy (Takayasu's disease) associated with 33 pregnancies and deliveries were followed up prospectively, from the prepregnant period. Inflammatory activity of the disease was apparently not enhanced by the pregnancy, but various cardiovascular-related events occurred in the perinatal period. During the intrapartum uterine contractions, marked elevation of systolic blood pressure was associated with 10 pregnancies, including 1 case of subsequent cerebral hemorrhage; this did not occur in 13 normal control gravidas. There were no maternal or neonatal deaths. The birth weight of 25 infants of 21 patients without complications or with a mild single complication of Takayasu's disease was 3,023 ± 442 g (mean ± standard deviation). The birth weight of 8 infants of 6 patients who had a severe single complication or multiple complications of the disease was 2,599 ± 394 g ($p < 0.05$). Of 83 pregnancies, the present 33 plus 50 other reported cases, there were no untoward events in two fifths. Three fifths had various problems, most of which were related to pressure elevation and heart failure, including intrapartum cerebral hemorrhage in 4. These data should assist in predicting the outcome of pregnancy and delivery in patients with Takayasu's disease.

Despite the tendency of occlusive thromboaortopathy (Takayasu's disease) to occur in women of the childbearing age, there is little information on the effect of pregnancy in these women or on the effects of the disease on pregnancy and its management. There are reports of 50 women with Takayasu's disease and 57 pregnancies,[1-38] including our previous reports of 7 pregnancies.[22,23] The great majority of reports, however, describe 1 or 2 cases and are short-term studies. From these studies, it is difficult to predict the incidence and type of complications and whether a pregnant woman with the disease will have an uncomplicated or complicated course.

Takayasu's disease is a chronic inflammatory arteriopathy of unknown origin.[39] The site of occurrence is the aorta or its main branches, or both; the pulmonary artery is often involved. The nature of the disease gives rise to 4 main complications: Takayasu's hypotensive ischemic retinopathy, secondary hypertension, aortic regurgitation, and aortic or arterial aneurysm.[40] The prognosis in patients with severe single or multiple complications is poorer than that in patients with only mild complications or without complications altogether.[41] Consequently, the problems related to pregnancy and delivery are superimposed on the established cardiovascular complications and inflammatory activity of the disease. Thus, a cardiologist is often consulted to evaluate the risks of pregnancy, labor, and delivery and the condition of fetus.

The clinical course of 33 pregnancies and deliveries in 27 Japanese women with Takayasu's disease and the follow-up studies are reported herein. The influence of pregnancy, labor, and delivery on the clinical course of the disease and the effects of the disease on pregnancy are analyzed. The pregnancies discussed herein, in addition to 50 other pregnancies in 46 patients with Takayasu's disease, are reviewed and the management is discussed.

Methods

Patient selection: During the 16 year period from April 1966 to January 1982, we treated 27 Japanese patients and a total of 33 pregnancies and deliveries, including 6 previously reported patients and 7 deliveries[22,23] (Table I). One pregnancy and the subsequent delivery was studied in 21 patients and 2 pregnancies were followed in 6 patients. The average age (± standard deviation) at the time of delivery in these 33 women was 28 ± 3 years. The average age at the time of onset of symptoms of Takayasu's disease and at the time of the diagnosis in the 27 patients was 19 ± 5 years and 23 ± 4 years, respectively. Of the 27 patients, 17 were admitted to the Third Department of Internal Medicine, Kyoto University, where the diagnosis of Takayasu's disease was established. These 17 women became pregnant during a follow-up period of 5.3 ± 3.7 years (mean ± standard deviation) after the diagnosis was established. In the remaining 10 patients, the diagnosis was confirmed after referral to our vascular outpatient clinic from other institutions.

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TABLE I Summary of 33 Pregnancies in 27 Japanese Women With Occlusive Thromboaortopathy (Takayasu's Disease) and the 33 Infants: Prepregnant Status, Obstetric Course, Major Treatments, and Birth Weight

Case	Age (yr)		Classifications at Time of Diagnosis		Disease Activity Before Pregnancy	Treatment During Pregnancy	Major Events During Pregnancy Labor, and Puerperium	Gestation (wk)	Mode of Delivery	Infant Weight (g)
	At Diagnosis	At Delivery	Grouping According to Complications	Anatomic Types						
Patients in Groups I and IIa Before Pregnancy (25 Pregnancies in 21 Patients)										
I-3	16	31 (PP)	IIa: SH	Arch	Inactive	0	Prolonged labor	39	CS	2,659
I-8	22	31 (PP)	I	Extensive	Inactive	0	↑BP, headache	40	CS	2,820
I-11	21	25 (PP)	IIa: SH	Extensive	Inactive	0	Preeclampsia	38	CS	2,350
I-14	28	31 (MP)	IIb: SH	Extensive	Inactive	D	CHF	39	Vacuum	3,522
I-15	22	28 (PP)	IIb: SH	Extensive	Inactive	D	0	36	Vacuum	2,650
I-17	19	28 (PP)	IIb: TR	Extensive	Active	0	↑BP in labor cerebral hemorrhage	37	Vacuum	2,900
I-18	19	23 (PP)	IIa: SH	Extensive	Inactive	Anticoagulant	↑BP in labor	41	Vacuum	3,550
		25 (MP)	...	...	Inactive	Anticoagulant	↑BP in labor	41	Vaginal	3,440
I-29	22	30 (PP)	I	Arch	Inactive	0	0	42	Vaginal	2,980
		32 (MP)	...	...	Inactive	0	0	39	Vaginal	2,950
O-1	27	29 (PP)	IIb: SH	Extensive	Inactive	Anticoagulant, D	Postpartum bleeding	37	Vacuum	2,360
		31 (MP)	...	...	Inactive	Reserpine, D	↑BP in labor	39	Vaginal	2,800
O-2	25	25 (PP)	IIa: SH	Extensive	Unknown	0	CHF after delivery	39	Forceps	3,650
I-35	22	26 (PP)	IIa: SH	Extensive	Inactive	0	0	41	Vaginal	3,670
I-38	26	30 (MP)	I	Arch	Active	0	0	41	Vaginal	3,300
O-5	23	26 (PP)	IIa: SH	Extensive	Suppressed	Prednisolone, reserpine	Preeclampsia ↑BP in labor	39	Vacuum	2,810
I-54	27	29 (MP)	IIa: SH	Extensive	Inactive	0	Puerperal septicemia	37	CS	2,980
		32 (MP)	...	...	Inactive	0	FUO in puerperium	37	CS	3,500
I-65	30	32 (MP)	I	Extensive	Active	0	Preeclampsia, CPD	40	CS	3,960
I-72	24	27 (PP)	I	Extensive	Suppressed	Prednisolone	↑BP in labor	40	Vacuum	2,970
I-73	27	30 (PP)	I	Arch	Suppressed	Prednisolone	0	39	Vacuum	2,920
O-7	25	32 (MP)	I	Extensive	Active	D	0	36	Vaginal	2,330
O-8	22	29 (PP)	I	Extensive	Suppressed	Prednisolone	0	39	Vaginal	2,820
I-88	27	27 (MP)	I	Extensive	Active	0	↑BP in labor	39	Vaginal	2,650
I-90	23	23 (PP)	IIa: TR	Extensive	Active	0	↑BP in labor	41	Vacuum	3,040
Patients in Groups IIb and III Before Pregnancy (8 Pregnancies in 6 Patients)										
I-12	17	24 (PP)	I*	Extensive	Active	Anticoagulant	Syncope	39	CS	2,420
		26 (MP)	...	...	Active	0	0	40	CS	2,765
I-13	20	31 (PP)	IIb: SH	Extensive	Inactive	Reserpine, D	↑BP in labor	38	CS	2,035
O-3†	20	28 (PP)	IIb: TR	Arch	Inactive	Anticoagulant, D	Preeclampsia	39	Vaginal	2,080
		37 (MP)	...	...	Inactive	0	0	39	Vacuum	3,050
I-47	23	31 (PP)	IIb: TR	Arch	Inactive	0	↑↓BP during anesthesia	39	CS	2,740
O-4	18	25 (PP)	IIb: TR	Arch	Inactive	D		38	Vaginal	2,640
O-6	20	24 (PP)	III: AR, SH, TR	Extensive	Suppressed	Prednisolone	0 Worsened ↑BP	40	Vaginal	3,065

* This case belonged to Group IIb: TR before pregnancy. † The case of left hemiparesis as sequelae of cerebral thrombosis at age 18.

AR = aortic regurgitation; BP = blood pressure; CHF = congestive heart failure; CPD = cephalopelvic disproportion; CS = Cesarean section; D = diuretic; FUO = fever of unknown origin; MP = multipara; PP= primipara; SH = secondary hypertension; TR = Takayasu's retinopathy.

In 24 of the 27 patients, angiography was performed; in the remaining 3, the diagnosis of Takayasu's disease was made clinically. The pulmonary circulation in 21 patients was studied using pulmonary arteriography, cardiac catheterization, and perfusion lung scanning in 10, and with perfusion lung scanning alone in 11.

Patient classification: To evaluate the disease status in detail, the following 3 factors were used: complications attributed to Takayasu's disease, sites of arterial lesions, and inflammatory activity of the disease as determined by the erythrocyte sedimentation rate.

Complications: The 27 patients were classified into 4 groups (Groups I, IIa, IIb, and III) according to the presence and severity of 4 complications attributed to Takayasu's disease at the time the diagnosis was established. The criteria for this classification were previously reported,[40] except for a slight modification of the criteria concerning severity of Takayasu's retinopathy.[41,42] As a rule, the severity of aortic regurgitation was assessed angiographically.[43] The aortographic grades of 3+ and 4+ were defined as severe aortic regurgitation. Retinal arterial pressure and blood pressure in the arms was measured with the women in the supine position. The prone position was used for pressure measurement in the thighs. During the third trimester, labor, and delivery, the pressure measurement in the thighs was usually performed with the patient in the supine position. During labor and vaginal delivery, analgesia and anesthesia were not given, except in a few cases.

All but 3 of 27 patients were reclassified clinically before the pregnancy or during the early period in the first trimester. As a result, 5 patients were improved: 4 from Group IIb to Group I or IIa, and 1 from Group IIa to I. On the other hand, aggravation was evident in 2 patients: 1 from Group I to IIa and 1 from Group I to IIb. Findings in the remaining 17 patients remained unchanged.

Sites of arterial lesions: According to the location of arterial lesions, the disease was anatomically classified into 3 types[44–46]: (1) aortic arch type, (2) descending aorta type, or (3) extensive type (combined aortic arch and descending aorta type). Of the 27 patients, 7 had aortic arch type disease and 20 had the extensive type at the time of the diagnosis. The descending aorta type was not detected in any patient.

Inflammatory activity: When erythrocyte sedimentation rate (Westergren) was consistently ≥20 mm/hour, inflammatory activity of Takayasu's disease was defined as the active stage, except during pregnancy and 6 weeks after delivery. Of 16 patients in the active stage at the time of diagnosis, 10 became inactive or the inflammatory activity was suppressed, and 6 remained unchanged before pregnancy. Eight patients in the inactive stage remained unchanged. In the remaining 3, the diagnosis of Takayasu's disease was first made during pregnancy.

Criteria for markedly elevated systolic pressure during intrapartum uterine contractions: By our definition, a markedly elevated systolic blood pressure during uterine contractions with bearing down efforts in the second stage of labor meant a maximum elevation of ≥70 mm Hg over the values between uterine contractions in the first stage of labor, or those before initiation of labor. In the first stage of labor, a markedly elevated systolic pressure during the height of a uterine contraction indicated a recurrent increase of ≥40 mm Hg. As a control group for the intrapartum pressure values, 13 healthy pregnant women were selected at random from patients hospitalized in our institution. These women had a normal antepartum course and a normal spontaneous labor at term with delivery of a living fetus; analgesia or anesthesia was not administered. Measurement of brachial blood pressure was performed consistently by 1 of the authors with the patient in the supine position. In the first stage of labor, blood pressure was measured when the cervix was dilated 4 to 8 cm.

Criteria for evaluating effects of pregnancy on the patient: Pregnancy was considered to have an unfavorable effect on patients with Takayasu's disease when Group I, IIa and IIb, or III progressed by 1 or more during pregnancy and the puerperium. A favorable effect was found when the classification improved by 1 or more groups. An occurrence of major events (Table I) also was considered an unfavorable effect. From the standpoint of inflammatory disease activity, the following were considered unfavorable: (1) an increase of ≥30 mm above the prepregnancy values of erythrocyte sedimentation rate per hour during the first half of the pregnancy and an increase of ≥60 mm in the second half; (2) an increase of 20 mm or more above the prepregnancy values over 6 weeks after delivery. A decrease of ≥20 mm under the prepregnancy values indicated a favorable effect.

Definition of preeclampsia, superimposed preeclampsia, and low birth weight: Preeclampsia and superimposed preeclampsia were defined according to the Committee on Terminology of the American College of Obstetricians and Gynecologists[47]: preeclampsia—development of gestational hypertension with proteinuria, edema, or both, after the 20th week of gestation; superimposed preeclampsia—occurrence of preeclampsia in a woman with antecedent hypertension. Criteria for the diagnosis of gestational hypertension were defined as a rise in systolic blood pressure of ≥30 mm Hg, or a rise in diastolic pressure of ≥15 mm Hg, or an absolute level of ≥140/90 on 2 occasions at least 6 hours apart. Low birth weight (a birth weight of 2,500 g or less) was defined according to the World Health Organization Expert Committee on Maternal and Child Health.[48]

Evaluation of pregnancy potential in the total population with the disease: During the 25 year period from 1957 to 1982, 90 patients admitted to the Third Department of Internal Medicine at Kyoto University were diagnosed as having Takayasu's disease. Of the 90 patients, 38 were selected for an evaluation of pregnancy potential in patients with Takayasu's disease, including 19 of the 27 patients in the present series. The remaining 52 patients were excluded from the study on pregnancy potential: 10 men, 18 unmarried women, 18 mothers of 2 or more children before the time of onset of symptoms of Takayasu's disease, and 6 married women using birth control methods but not birth control pills. (These 6 were excluded for a recurrent hemoptysis, a postoperative status of aortic bypass graft, a giant aneurysm of the ascending aorta (operative death), a continuance of corticosteroid therapy with a large daily dose, and economic difficulties [2].)

Statistical analysis: Statistical comparisons were made using the t test, the paired t test, and the chi-square method with the Yates correction for continuity.

Results

Classification and distribution of patients: The 27 patients were reclassified before pregnancy or during an early period in the first trimester of pregnancy. Combined Groups I and IIa comprised 21 patients (77.8%) and combined Groups IIb and III, 6 patients (22.2%). Of the 21 patients in whom pulmonary circulation was studied, 10 had involvement of the pulmonary artery.

Effect of pregnancy: The effect of pregnancy, labor, and delivery on the clinical course of Takayasu's disease is shown in Figure 1. Most of the unfavorable effects

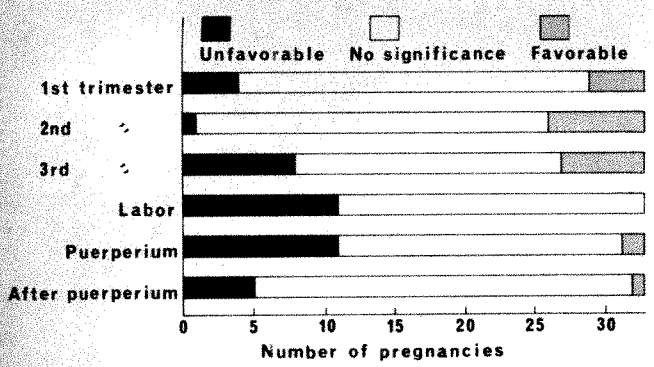

FIGURE 1. Effect of 33 pregnancies in 27 patients with occlusive thromboaortopathy. In 33 pregnancies, 4 (12.1%), 1 (3.0%), 8 (24.2%), 11 (33.3%), 11 (33.3%), and 5 (15.2%) had an unfavorable effect during the first trimester, second trimester, third trimester, labor, puerperium, and postpuerperium, respectively.

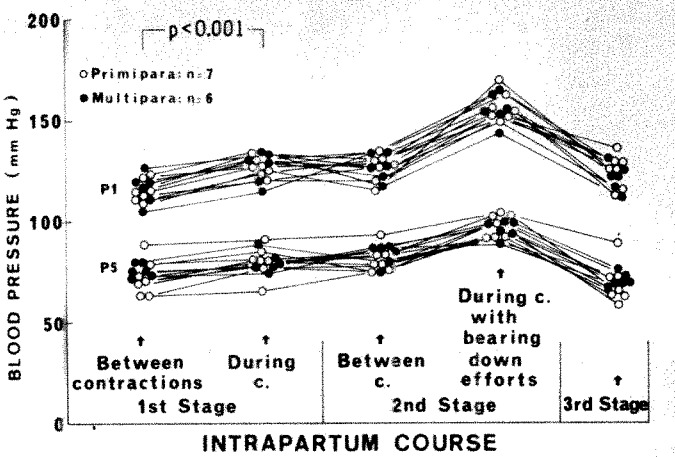

FIGURE 2. Blood pressure between and during uterine contractions in the intrapartum course in 13 healthy women. Measurements were obtained both during a complete uterine relaxation and during the height of a contraction. In each woman, the blood pressure value during each stage of labor and each phase of contraction was expressed as mean values obtained at 3 or more uterine contraction cycles. P1 = systolic pressure; P5 = diastolic pressure; p = probability.

were noted in the perinatal period. The second trimester of pregnancy was the most stable. There were no maternal deaths. Of the 33 pregnancies, 22 (66.7%) had an unfavorable effect and the remaining 11 (33.3%) were uneventful during the entire obstetric course. There was no significant difference in the incidence of an unfavorable effect during each period of the entire course between combined Groups I and IIa and combined Groups IIb and III (chi-square method). In all pregnancies, an inflammatory activity of the disease was not obviously affected by the pregnancy, even in a patient in the severe active stage (>100 mm/hour of erythrocyte sedimentation rate before pregnancy); in fact, there was a transient improvement in 5. There were no pattern changes in the group during pregnancy and the puerperium, except for 3 patients whose mild or moderate hypertension before pregnancy was transiently normalized. The grade 2/6 early diastolic murmur of aortic regurgitation before pregnancy became inaudible during the antepartum period in 1 patient. The same intensity of murmur became audible 3 weeks after delivery. The major events which developed during pregnancy, labor, and the puerperium are shown in Table I. There were differences in the character of the events in each period. In general, events due to cerebral ischemia occurred in the first trimester of pregnancy and the postpartum period, and cardiovascular events occurred in the perinatal period. An unfavorable effect remained in 5 patients after the puerperium, but permanent sequelae occurred in only 1 woman who had an intrapartum cerebral hemorrhage (Case I-17). Left temporal craniotomy and evacuation of the left intracerebral hematoma (lateral type) were successfully performed 20 hours after delivery.

In 13 healthy pregnant women whose average age (± standard deviation) was 29 ± 5 years, the response of blood pressure to uterine contractions during labor is shown in Figure 2. The value of blood pressure between and during uterine contractions in the first stage of labor was 116 ± 6/74 ± 7 mm Hg (mean ± standard deviation [SD]) and 127 ± 6/80 ± 7 mm Hg, respectively ($p < 0.001$). During uterine contractions with bearing down efforts in the second stage of labor, the average value of systolic pressure (± SD) was 156 ± 7 mm Hg. When the latter was calculated using the maximal value obtained in each gravida, it was 168 ± 9 mm Hg (range 150 to 186). There was no incidence of a rise in systolic pressure of ≥70 mm Hg in maximum over the pressure values between uterine contractions in the first stage of labor, in any patient. Regarding the blood pressure values obtained during labor in patients with Takayasu's disease, 10 pregnancies of the comparable 22 (4 in patients with arch type disease, 18 in patients with the extensive type) had markedly elevated systolic pressure during uterine contractions. In these 10 pregnancies, the response of blood pressure to uterine contractions during

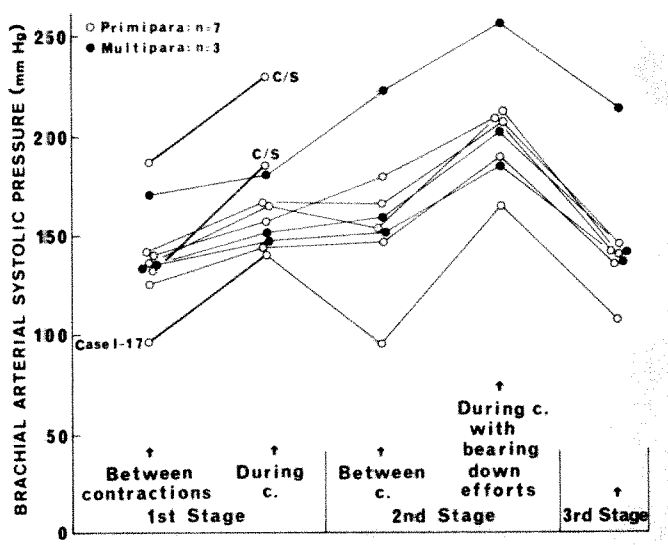

FIGURE 3. Brachial arterial systolic pressure in the intrapartum course in 10 pregnant women with Takayasu's disease and a marked pressure increment during uterine contractions. Blood pressure was expressed as mean values, as in Figure 2. CS = cesarean section.

labor is shown in Figure 3. The incidence of a marked increase in pressure in the 22 pregnancies was significantly greater than that (none) in the normal 13 pregnancies ($p < 0.025$). There was no significant difference in the average age at the time of delivery in the 2 groups (t test). The 10 patients with a marked pressure increase had the extensive type of disease and included 5 with preexisting secondary hypertension and 5 normotensive patients, not only before pregnancy but also during the antepartum period. Of the former, 1 had a superimposed preeclampsia in the third trimester; in 1 of the latter a cerebral hemorrhage occurred just before delivery (Fig. 4).

Treatment and management during pregnancy: During pregnancy, labor, delivery, and the puerperium, treatment included corticosteroids, anticoagulants, and symptomatic therapy for which antihypertensive agents, digitalis, and antibiotics were frequently used. Nonsteroidal anti-inflammatory agents were rarely prescribed. In 5 of the 27 patients, small doses (5 to 12.5 mg/day) of prednisolone, which the patients were taking at the time of conception, were continued throughout pregnancy, except for 1 patient who stopped taking prednisolone during pregnancy and in whom the inflammatory activity was increased after the puerperium. In another patient in the severe active stage before pregnancy, corticosteroid therapy with an initial daily dose of 50 mg of prednisolone was begun 14 weeks after delivery. Among 4 pregnant women receiving oral anticoagulant therapy (anisindione), 1 had macrohematuria in the third trimester and another had a postpartum hemorrhage. In 4 patients and 5 pregnancies, hospitalization was prescribed during the period from 23 to 36 weeks' gestation.

Follow-up after delivery: The 27 patients were followed up prospectively for observation periods of 5.9 ± 4.3 years (mean ± SD) from the time after the delivery to January 1982. Of the 27, 1 was lost to follow-up after 6 months and 1 died from a cerebrovascular accident 6 years after delivery. The remaining 25 patients were living as of January 1982.

Effect of disease on pregnancy: fetal and neonatal outcome: Of the 33 pregnancies, 30 ended at full term, namely, between 37 and 41 completed weeks of gestation. In the remaining 3, 2 ended at 36 weeks' gestation and 1 ended at 42 weeks' gestation. The average time of gestation (± SD) was 39.0 ± 1.5 weeks. Of 45 pregnancies during the period from onset of symptoms of Takayasu's disease to the present successful delivery in the 27 patients, 2 patients had pregnancy which ended in spontaneous abortion at 10 or 11 weeks' gestation. One other patient had a history of 2 preterm stillbirths (30 and 33 weeks) and 2 spontaneous abortions (both 13 weeks). There were no therapeutic abortions. No neonatal death or congenital anomaly occurred in the 33 infants. The average birth weight (± SD) of the 33 was 2,920 ± 463 g; 6 of the 33 (18.2%) were low birth weight but full term, except 1 (36 weeks). The birth weight of 25 infants of 21 patients in combined Groups I and IIa and that of 8 infants of 6 patients in combined Groups IIb and III was 3,023 ± 442 g (mean ± SD) and 2,599 ± 394 g, respectively ($p < 0.05$). Regarding gestational age of the infants, there was no significant difference between the 2 combined groups. Of the 33 infants or children, 32 were living as of January 1982, with an average age (± SD) of 5.9 ± 4.6 years. (One child was lost to follow-up 6 months after birth.)

Method of delivery: Twelve of the 33 deliveries (36.4%) were normal vaginal deliveries. Vacuum extraction was performed in 10 instances (30.3%) to expedite the second stage of labor because of fetal distress in 2, markedly elevated systolic pressure during uterine contractions with bearing-down efforts in 5, and antecedent hypertension in 3. Forceps were used in 1 (3.0%). In the remaining 10 deliveries (30.3%), cesarean section was performed for obstetric indications in 6 and for nonobstetric indications in 4. The latter included markedly elevated systolic pressure during intrapartum uterine contractions in 2 patients (Cases I-8 and I-13), superimposed preeclampsia in 1 (Case I-11), and extremely severe aortic arch type with unobtainable blood pressure in either arm in 1 (Case I-47) (Table I).

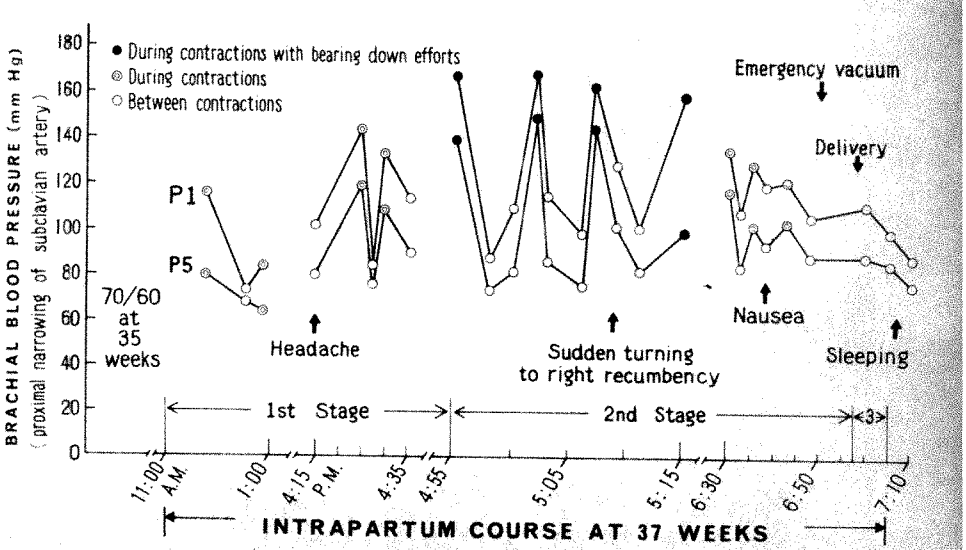

FIGURE 4. Intrapartum time course and right brachial blood pressure with narrowing of the ipsilateral subclavian artery at age 28 years in Patient I-17, in whom cerebral hemorrhage occurred in the second stage of labor. The actual systemic blood pressure was probably more elevated during uterine contractions, compared with values obtained in the right brachial artery. P1 = systolic pressure; P5 = diastolic pressure.

Pregnancy potential: Of the 38 patients with Takayasu's disease selected for evaluation of pregnancy potential, 30 (78.9%) were delivered of a live infant less than 3 years after the period filling the requirements of both occurrence of the basic disease and pregnancy. Five patients (13.2%) were delivered of 1 infant during the period from 3.3 to 6.5 years and the remaining 3 (7.9%) did not become pregnant, even in the absence of birth control practices, except for 1 patient who had 2 abortions. Table I summarizes the results of 33 pregnancies in the 27 patients.

Discussion

Effect of pregnancy on the patient: In this series, we found that the underlying disease activity, as reflected by the erythrocyte sedimentation rate, was not acutely affected by the pregnancy, regardless of an active or inactive stage before the pregnancy. In contrast, various cardiovascular events developed during pregnancy, labor, and the puerperium. A search of the world literature revealed 57 pregnancies in 52 patients with Takayasu's disease, most of which were reported by obstetricians.[1–38] Our evaluation of the effect of pregnancy, labor, and delivery on the disease was made according to the criteria described in the section on methods. Of the present 33 pregnancies and of the previously reported 50 (excluding our previously reported 7[22,23]), 51 (61.4%) had an unfavorable effect, including 4 deaths (4.8%); the remaining 32 (38.6%) were uneventful. Of 83 pregnancies, 11 (13.3%), 10 (12.0%), 31 (37.3%), and 23 (27.7%) had an unfavorable effect during the first, second, and third trimester and labor, respectively. The effect was unfavorable during the puerperium in 30 of 81 (37.0%). However, the unfavorable effect continued beyond the puerperium in only 5 pregnancies (15.2%) in the present series.

Of the maternal events, those related to elevation of blood pressure (regardless of the presence or absence of hypertension before pregnancy) and heart failure were the most frequent. These events usually were prominent in the perinatal period and were attributed to (1) heart failure and cerebrovascular accidents as the usual major factors related to death in nonpregnant patients with Takayasu's disease,[40,41] (2) the imposition of an increased cardiac load in the perinatal period on the underlying nature of the disease,[49–56] and (3) concomitant and extremely rapid changes in the cardiovascular system,[57–61] including fluctuations of blood pressure during the intrapartum and the subsequent course.

Intrapartum blood pressure and cerebral hemorrhage: In general, there is a paucity of data regarding the response of blood pressure to second stage contractions with bearing-down efforts.[58–61] Winner and Romney,[60] using invasive methods, reported increments of systolic pressure above resting levels from 15 to as high as 75 mm Hg during second stage contractions with expulsive efforts in normal gravidas. Their results, in which the maternal posture at the time of the measurements was not given, were similar to our data—an increase of up to 28 to 64 mm Hg, obtained in normal gravidas who were in the supine position (Fig. 2). In our pregnant patients with Takayasu's disease, the incidence of an abnormal response of systolic pressure to intrapartum uterine contractions, particularly to second stage contractions with bearing-down efforts, was significantly greater than in the normal control gravidas. The marked increase in pressure was not found in patients with the arch type of disease but in those with the extensive type. Therefore, such susceptibility of blood pressure to the marked elevation under these conditions may be partly related not only to the baroreceptor dysfunction of the carotid sinuses and the reduced windkessel effect of the involved aorta,[62,63] but also to a narrowing effect of the descending aorta.

Intracerebral hemorrhage during labor in patients with Takayasu's disease occurred in 4 patients, including 3 reported by Takeshita et al,[30] Miyakoshi et al,[34] and Takashina et al[35] and 1 of our patients (Case I-17). These 3 patients died. The 4 patients had the following characteristics in common: (1) extensive and severe occlusion, narrowing, or both of the main branches arising from the arch of the aorta, (2) marked increase in blood pressure in the first stage of labor, except for 1 patient in whom pressure measurement in any extremity could not be obtained, (3) presence of headache or nausea as a prodromal symptom, (4) occurrence of bleeding before delivery of the infant (at the first stage of labor in the 3 previously reported cases and at the second stage in our case), and (5) a history predisposing to classification into Group IIb or III in Takayasu's disease during the prepregnant course. In our 9 ptients with an intrapartum marked elevation of systolic pressure but no cerebral hemorrhage, cervical arterial lesions were not so severe as the lesions related to retinal arterial microaneurysms. Thus, the intrapartum cerebral hemorrhage in patients with Takayasu's disease may be due in part to a combination of severity of intrapartum elevation of central blood pressure and of antecedent cerebral ischemia. In general, intracerebral hemorrhage during labor rarely occurred even in pregnant patients with cerebral arterial aneurysm or angioma,[64] congenital coarctation of the aorta,[65] and chronic hypertension or superimposed preeclampsia.[66] Takayasu's disease is one of the diseases associated with intrapartum cerebral hemorrhage.

Evaluation of the disease as related to the risks of pregnancy: There was no significant difference in incidence of an unfavorable effect of pregnancy on the basic disease between patients in combined Groups I and IIa and those in combined Groups IIb and III. However, these results may be due in part to the influence of elective cesarean section, prophylactic management, or both, particularly in patients in Group IIb (Cases I-13 and I-47). Patients with the extensive type and retinal microaneurysms or a history before pregnancy may have intrapartum cerebral hemorrhage. According to previous reports,[41] among patients in Group IIb or III, those with a severe disability had the poorest prognosis. Therefore pregnancy in these patients should be avoided, interrupted, or continued under conditions of hospitalization. In the present series, there was only 1 such severe case (Case I-13). During pregnancy, aortic regurgitation[67] and high blood

pressure[68,69] in some patients with Takayasu's disease may be underestimated or overlooked. Variations of blood pressure responses during pregnancy, apart from the blood pressure response during labor in prepregnant hypertensive patients with Takayasu's disease, were similar to those in patients with essential hypertension.[68]

Medical, obstetric, and anesthetic therapy or management: Medical treatment of pregnant patients with Takayasu's disease may not differ essentially from that of the nonpregnant patients, except for obstetric considerations. Oral anticoagulant therapy should be postponed because of maternal and fetal hazards[70] until the puerperium, when nursing mothers given warfarin may safely breast-feed their infants.[71] Regarding maternal corticosteroid therapy, it has been suggested that the fetus is seldom affected by the therapy,[72,73] although some investigators[74,75] have reported adverse effects. In our series, there were no obvious maternal and fetal risks arising from the use of prednisolone in 5 patients prescribed a small, daily dose. Of the 5, 1 patient discontinued the drug during pregnancy and the inflammatory activity of the disease was considerably increased after the puerperium, as compared with before the pregnancy. Therefore, the small daily dose of prednisolone ingested before pregnancy should be continued during pregnancy. We recommend that initiation of a large daily dose of prednisolone during pregnancy be postponed until the postpuerperal period. Except for a patient with fulminant progression of arterial occlusive changes, commencement of this therapy after the puerperium may be effective, even in a patient with very high inflammatory activity of the disease (Case O-7). Prophylactic antibiotics should be used at the time of delivery in all patients, particularly in patients on corticosteroid therapy, in order to prevent bacterial endocarditis or septicemia not only because of aortic regurgitation but also because of narrowing of the aorta and its main branches. Septicemia occurred in 1 patient after cesarean section (Case I-54). Oral contraceptives should be avoided, as there may be adverse effects on patients with Takayasu's disease.[76] In this series, no patient was taking oral contraceptives.

For management of blood pressure, clinical evaluations of pressure values obtained in the extremities are most important not only to the physician but also to the obstetrician and anesthesiologist because (1) the pressure measurement in the arteries distal to the site of narrowing of the aorta and its main branches does not always give the "actual" blood pressure; (2) pressure measurement in the legs is not always practical in the second stage of labor; and (3) a slight decrease in blood pressure in patients with extensive and severe occlusive lesions of main cervical arteries frequently leads to syncopal attack or to severe cerebral ischemia. Elective cesarean section for nonobstetric indications may be recommended for the following patients: (1) in Groups IIb and III, particularly in those with severe Takayasu's retinopathy in the extensive type of the disease, if they have markedly elevated systolic blood pressure (defined earlier) during uterine contractions in the first stage of labor, (2) in Groups IIb and III if pressure measurement cannot be obtained in either arm, (3) in Groups I and IIa if they have markedly elevated systolic pressure with symptoms in the first stage of labor, despite medical treatment. In vaginal delivery, the second stage of labor can be shortened using a vacuum extractor or forceps. Intravenous injection of uterotonic agents, particularly ergonovine maleate,[77] should be avoided or at least closely monitored because of occurrence of increased dyspnea or cyanosis in some patients with Takayasu's disease.[1,17,21] Anesthetic considerations in this disease have been well summarized.[78]

Fetal outcome and fertility: In the present series, there was no increase in fetal mortality and no particular tendency toward spontaneous abortion in patients with Takayasu's disease. However, the incidence of low birth weight (2,500 g or less) was 18.2% (6 of the 33 infants), and the value may be higher than the 9.0% incidence in Japan in 1952.[79] The average birth weight of infants of the patients in combined Groups IIb and III was significantly lower than that of infants of the patients in combined Groups I and IIa. Among the 8 pregnancies in the former combined groups, 6 belonged to Group IIb and had signs of severe Takayasu's retinopathy. Therefore, the intrauterine growth retardation of the fetus in patients with Takayasu's disease may be related in part to severity of heart failure[80,81] and hypertension,[82] and cerebral ischemia in which Takayasu's ischemic retinopathy may be representative. As described in the section of pregnancy potential, fertility is apparently not affected by the disease, although it was suggested that a patient with this disease often has an anovulatory menstruation due to hormonal imbalance.[83]

Implications: The basic disease was not obviously affected by the pregnancy. However, the cardiovascular complications attributed to Takayasu's disease were transiently modified in many and often seriously enhanced in some patients. To prevent expected events or further enhancement of events already present, the following are important: (1) a prepregnant evaluation of the individual's basic disease, as related to risks and safety of pregnancy, (2) careful management during the periods when untoward events may occur, (3) planning the mode of delivery from both obstetric and nonobstetric indications, and (4) the intrapartum and anesthetic considerations with special reference to the measurement and management of blood pressure. Close cooperation among the cardiologist, obstetrician, and anesthesiologist is indispensable to successful pregnancy, labor, delivery, and puerperium in the woman with heart disease,[84] particularly Takayasu's disease.

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Left Ventricular End-Systolic Stress-Shortening and Stress-Length Relations in Humans

Normal Values and Sensitivity to Inotropic State

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Experimental studies suggest that the extent of left ventricular (LV) fiber shortening is determined by both the wall stress at end-systole and the contractile state. To evaluate the relation between these variables assessed noninvasively, 26 normal subjects were studied by M-mode echocardiography, phonocardiography, and indirect carotid pulse tracings during infusion of methoxamine to alter load (in all 26 subjects) and infusion of dobutamine (in 10 subjects) to increase contractility. End-systolic pressure was estimated from the incisura of a calibrated carotid pulse tracing. LV end-systolic dimension and wall thickness, and percent internal dimension shortening were determined by echocardiography, and end-systolic meridional wall stress was calculated. The relation between end-systolic stress and shortening was inversely linear ($r = -0.83$) for 130 control points. Dobutamine infusion resulted in a higher percent fractional shortening for any end-systolic stress; all 43 stress-shortening points were more than 2 standard deviations above the mean for the regression line. The relation between stress and dimension for the control points showed wider scatter than between stress and shortening ($r = 0.56$). However, in individual patients dobutamine always shifted the stress-dimension lines to the right, as compared with the baseline position resulting in a smaller end-systolic dimension for any end-systolic wall stress.

Thus, LV end-systolic wall stress and percent fractional shortening are inversely and linearly related and their relation can be accurately assessed by noninvasive methods. The end-systolic stress-shortening relation is highly sensitive, while the end-systolic stress-dimension relation is less sensitive to alterations in LV inotropic state.

The assessment of intrinsic LV contractile state, particularly by noninvasive means, remains a complex and controversial problem. The most commonly used clinical measurements of LV contractility are the ejection fraction, the percent fractional shortening, and the rate of change of LV wall thickening or dimension during systole. These ejection phase indexes, however, are affected importantly by the heart's loading condition and vary directly with end-diastolic fiber length (preload) and inversely with afterload.[1-4] Their clinical utility is limited by a wide range of normal values and the inability to distinguish between the mechanical effects of abnormal loading conditions and intrinsic depression in an inotropic state.

Several alternative methods of assessing LV contractile state have recently been studied. It has been known for many years that the left ventricular isovolumetric force-length relation, which is dependent on contractile state, describes the maximal force attainable for any degree of myocardial stretch.[5,6] Experimental studies performed in isolated canine hearts have dem-

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onstrated that LV force-length relations obtained either isovolumetrically or at the end of ejection are virtually identical.[4,7–9] For any LV contractile state, shortening ceases when the active force-length relation coincides with a point on the isovolumetric force-length line. At this point, the LV wall force equals the maximal force that muscle length can sustain. In addition, for a given end-diastolic volume and contractile state, the end-systolic pressure-volume relation determines the extent of LV muscle shortening irrespective of the peak systolic pressure.[10] LV shortening ends when a unique relation between instantaneous systolic force and muscle length occurs. This relation is sensitive to contractile state, but is independent of end-diastolic fiber length as well as early or peak LV ejection forces. From these studies of basic cardiovascular physiology, the relation between LV end-systolic muscle length, force opposing shortening (wall stress), and extent of shortening appear potentially useful indexes of contractile state which incorporate afterload conditions.[11]

Recently, we reported a safe, easily performed noninvasive method of assessing LV function at end-systole.[12,13] In the present study, we used this method to evaluate end-systolic stress-shortening and stress-length relations in humans with emphasis on their normal relations as well as sensitivity to alteration in contractile state. This was accomplished by studying the response of the left ventricle to the alteration of loading conditions by the infusion of a pure alpha-adrenergic agonist without direct cardiac effect (methoxamine)[14,15] and to changes in the contractile state by infusion of a positive inotropic agent (dobutamine).[16,17]

Methods

Study population: The study population consisted of 26 healthy subjects (11 male, 15 female) ranging in age from 8 to 41 years, all of whom had no history of cardiovascular disease, were taking no cardioactive medications, and had normal physical examination, electrocardiogram, and intracardiac anatomy by M-mode echocardiography.

Experimental protocol: An Irex Continutrace Model 101 and ultrasound module with a 2.25 or 3.5 MHz transducer was used for the M-mode echocardiographic recordings. An external microphone was placed at the right upper sternal border area for phonocardiographic recordings. Peak systolic and diastolic blood pressure measurements were made with the Dinamap™ 845 Vital Signs Monitor (Critikon, Tampa, Florida). In a recently reported study,[18] we found that this device can estimate central aortic pressure accurately over a wide range of systolic (98 to 177 mm Hg) and diastolic (41 to 97 mm Hg) pressures, independent of the patient's cardiac index, systemic vascular resistance, left ventricular ejection fraction, heart rate, or body surface area. The mean percent error (± standard deviation) between simultaneously measured central and Dinamap pressures was 1 ± 4 mm Hg for systolic and 2 ± 4 mm Hg for diastolic readings.

Subjects were premedicated with intravenous atropine, 0.01 mg/kg, to abolish reflex cardiac slowing. Each subject underwent simultaneous recordings of systolic and diastolic blood pressures, echocardiography of the left ventricle, phonocardiography, indirect carotid pulse tracing, and electrocardiography under baseline conditions. Blood pressure was then elevated by the intravenous infusion of methoxamine at 25 μg/kg/min (maximal infusion rate 1 mg/min). The LV response to the pressor challenge was assessed by repeating the recordings every 1 to 2 minutes during the infusion. When peak systolic pressure had increased by 30 to 60 mm Hg above the resting values, the methoxamine infusion was discontinued. The peak pressor effect lasted 2 to 5 minutes. When systolic blood pressure had fallen by 15 to 20 mm Hg below the peak value, an intravenous infusion of 5 μg/kg/min of dobutamine hydrochloride was begun in 10 of the subjects. As the pressor effect of methoxamine further decreased with metabolism of the drug, the LV response to the positive inotropic intervention was recorded over a range of afterload conditions. In order to avoid the complicating effects of changes in heart rate, data points were excluded when the latter varied by more than 10 beats/min from baseline.

The echocardiographic LV end-diastolic internal dimension and end-diastolic wall thickness were measured at the onset of the Q-wave of the electrocardiogram while the end-systolic internal dimension and wall thickness were measured synchronously with the first high frequency component of the second heart sound. The measurements for end-diastolic and end-systolic dimensions and wall thicknesses were taken as the mean values for 5 cardiac cycles. LV percent fractional shortening (%ΔD) was calculated as follows: $\%\Delta D = (D_{ED} - D_{ES})/D_{ED}$, where D_{ED} is the end-diastolic and D_{ES} the end-systolic dimension. LV mid-wall end-diastolic and end-systolic dimensions were calculated as the internal dimension plus wall thickness at end-diastole and the internal dimension plus wall thickness at end-systole, respectively. This assumes that the septal and posterior wall surfaces of the left ventricle are of equal thickness. LV mid-wall percent fractional shortening ($\%\Delta D_{mw}$) was calculated as follows: $\%\Delta D_{mw} = (D_{ED_{mw}} - D_{ES_{mw}})/D_{ED_{mw}}$, where $D_{ED_{mw}}$ is the end-diastolic and $D_{ES_{mw}}$ the end-systolic mid-wall dimension. LV end-systolic and end-diastolic volumes were estimated from echocardiographic internal dimensions utilizing the method of Teichholz et al,[19] which assumes that the visualized portion of the left ventricle is representative of global ventricular function, an assumption previously shown valid in normal subjects in the absence of ventricular synergy. LV stroke volume was calculated as the end-diastolic minus end-systolic volumes; LV output was calculated as the product of stroke volume and heart rate. The accuracy of this method of estimating LV stroke volume in patients with symmetrical or nearly symmetrical contraction patterns is comparable to that obtained with single plane LV cineangiography.[20]

The carotid pulse tracings were calibrated using the automated blood pressure monitor device after the method of Stefadouros et al,[21] with systolic pressure assigned to the peak and diastolic pressure assigned to the nadir of the tracing. End-systolic pressure was estimated by linear interpolation to the height of the incisura. This method has been validated previously over a wide range of end-systolic pressures (84 to 160 mm Hg) in our cardiac catheterization laboratory against an intraarterial standard. The mean difference between direct and indirect pressure measurements was 3 mm Hg with a standard deviation of the difference of 4 mm Hg and a correlation coefficient of 0.97.[22]

LV meridional wall stress at end-systole was calculated using the angiographically validated method described by Grossman et al[23,24]: $\sigma_{ES} = [(P_{ES})(D_{ES})(1.35)]/[(4)(h_{ES})(1 + h_{ES}/D_{ES})]$, where σ_{ES} is end-systolic wall stress in g/cm^2; P_{ES} is end-systolic pressure in mm Hg; D_{ES} and h_{ES} are end-systolic dimension and wall thickness in cm; and 1.35 is the factor to convert pressure from mm Hg to g/cm^2.

TABLE I Hemodynamic Response to the Afterload Challenge

	Baseline	Peak Pressor Effect	p Value
Heart rate (beats/min)	90 ± 21	91 ± 22	NS
P_{PS} (mm Hg)	115 ± 7	163 ± 13	<0.001
P_D (mm Hg)	71 ± 10	103 ± 9	<0.001
P_{ES} (mm Hg)	94 ± 8	137 ± 10	<0.001
D_{ES} (cm)	3.10 ± 0.40	3.50 ± 0.40	<0.001
D_{ED} (cm)	4.65 ± 0.55	4.95 ± 0.55	<0.001
$\%\Delta D$	33.7 ± 2.2	30.0 ± 2.6	<0.001
$\%\Delta D_{mw}$	18.9 ± 1.9	18.4 ± 2.1	NS
SV (ml)	62 ± 12	64 ± 14	NS
CO (liters/min)	5.6 ± 1.3	5.8 ± 1.4	NS
h_{ES} (cm)	1.40 ± 0.20	1.25 ± 0.20	<0.001
σ_{ES} (g/cm^2)	50 ± 18	95 ± 30	<0.001

CO = cardiac output; D_{ES} = end-systolic dimension; D_{ED} = end-diastolic dimension; $\%\Delta D$ = percent internal dimension fractional shortening; $\%\Delta D_{mw}$ = percent mid-wall fractional shortening; h_{ES} = end-systolic wall thickness; P_{PS} = peak systolic pressure; P_D = diastolic pressure; P_{ES} = end-systolic pressure; σ_{ES} = end-systolic meridional wall stress; SV = stroke volume.

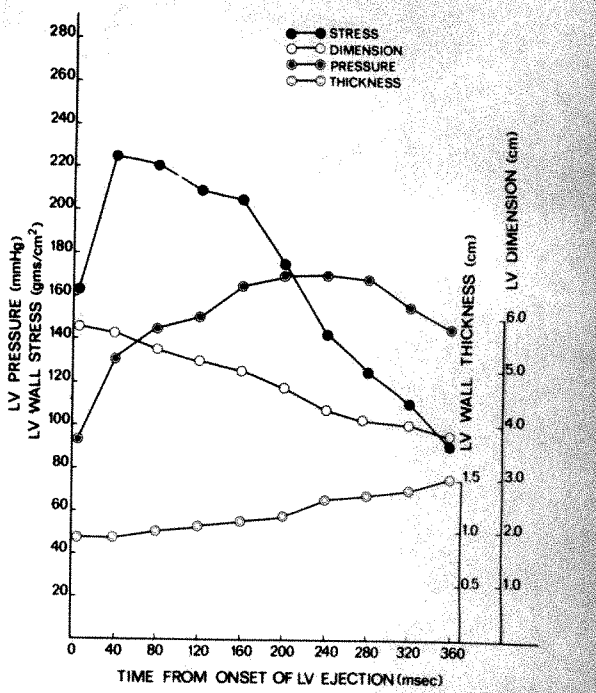

FIGURE 1. LV meridional wall stress calculated throughout ventricular ejection in a representative subject from simultaneous measurements of LV pressure, dimension, and wall thickness. Wall stress peaked early in ventricular systole and then declined throughout the remainder of the ejection period. The relatively long LV ejection time (370 ms) was due to the subject's slow heart rate (R-R interval 1330 ms).

All subjects were studied using a protocol approved by the Human Studies Committee of the Brigham and Women's Hospital and of the Children's Hospital Medical Center.

Data analysis: Simple linear regression (least squares method) was used to fit each subject's data to a stress-shortening ($\%\Delta D = m[\sigma_{ES}] + b$) and stress-length ($D_{ES} = m[\sigma_{ES}] + b$) equation, where m = the slope and b = the y intercept. The extrapolated LV end-systolic wall stress when end-systolic dimension is zero is equal to $-b/m$. In the 10 subjects who received the dobutamine infusion, a comparison of the LV response under control and increased inotropic conditions was performed using Student's t test for paired data. A p value <0.05 was taken as indicative of statistical significance. Unless otherwise noted, the data are presented as the mean ±1 standard deviation.

The 130 control end-systolic stress-shortening, stress–mid-wall shortening, and stress-dimension points were pooled and linear regression equations with 95% confidence limits (±2 standard deviations) determined for each relation. Any dobutamine points outside these limits were considered statistically different from the control population.

Results

LV hemodynamics: Table I summarizes the hemodynamic response to the afterload challenge for the 26 normal subjects. LV end-systolic dimension, end-systolic stress, and end-diastolic dimension varied directly

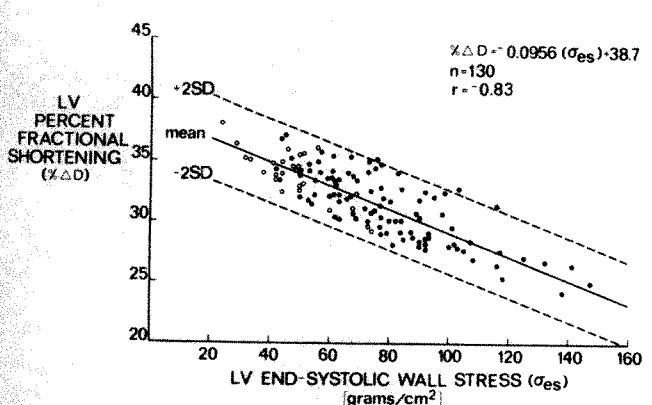

FIGURE 2. Relation between LV end-systolic wall stress (σ_{es}) and percent fractional shortening ($\%\Delta D$) for the 130 control points obtained at rest (**open circles**) or during methoxamine infusion (**closed circles**). LV σ_{es} and $\%\Delta D$ are inversely and linearly related over a wide range of values.

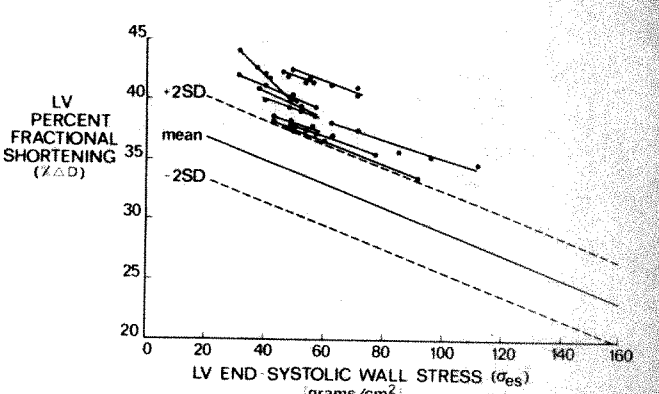

FIGURE 3. Plot of the LV end-systolic wall stress (σ_{es})-shortening ($\%\Delta D$) relation, showing its sensitivity to inotropic state. All of the σ_{es}-$\%\Delta D$ points obtained during the dobutamine infusion were greater than 2 standard deviations above the mean value for the regression line generated from the 130 control points.

TABLE II Data Matched for End-Systolic Pressure Showing Individual Response to Alteration in Inotropic State

Case	HR	D_{ES}	D_{ED}	% ΔD	h_{ES}	P_S	P_D	P_{ES}	σ_{ES}
1									
C	103	3.30	4.60	28.3	1.10	147	88	121	92
D	101	2.80	4.55	38.5	1.35	147	82	120	57
2									
C	46	3.80	5.45	30.3	1.50	165	92	146	90
D	60	3.25	5.55	41.4	1.75	165	89	138	56
3									
C	120	3.70	5.15	28.2	1.20	153	106	134	102
D	122	3.40	5.10	33.3	1.25	159	103	143	96
4									
C	106	3.85	5.35	28.0	1.50	161	106	140	85
D	129	3.40	5.45	37.6	1.70	155	100	129	56
5									
C	61	3.50	5.05	30.7	1.55	150	87	128	68
D	62	3.05	4.95	38.4	1.85	151	87	125	43
6									
C	88	3.90	5.30	26.4	1.10	168	101	151	141
D	108	3.35	5.20	35.6	1.45	177	99	155	85
7									
C	83	3.45	5.10	32.4	1.25	150	95	134	92
D	100	3.00	4.95	39.3	1.50	148	77	127	57
8									
C	87	3.70	4.95	25.3	1.10	151	101	135	118
D	93	2.90	4.90	40.8	1.30	164	92	136	71
9									
C	70	3.70	5.10	27.5	1.20	180	118	149	117
D	88	3.15	5.00	37.0	1.60	174	108	144	63
10									
C	101	3.20	4.45	28.1	1.05	137	84	117	90
D	115	2.45	4.05	39.5	1.30	139	87	119	49
Control									
Mean	87	3.60	5.05	28.5	1.25	156	98	135	99
SD	23	0.25	0.30	2.1	0.20	12	11	11	21
Dobutamine									
Mean	98	3.10	5.00	38.1	1.50	158	92	134	63
SD	23	0.30	0.45	2.4	0.20	12	10	12	16
p Value (C vs D)	<0.05	<0.001	NS	<0.001	<0.001	NS	<0.05	NS	<0.001

C = control; D = dobutamine; D_{ES} = end-systolic dimension (cm); D_{ED} = end-diastolic dimension (cm); % ΔD = percent fractional shortening; h_{ES} = end-systolic wall thickness (cm); HR = heart rate (beats/min); P_S = peak aortic systolic pressure (mm Hg); P_D = aortic diastolic pressure (mm Hg); P_{ES} = end-systolic pressure (mm Hg); σ_{ES} = end-systolic meridional wall stress.

whereas end-systolic wall thickness and percent fractional shortening varied inversely with increased ventricular pressure. Heart rate, stroke volume, and cardiac output remained unchanged.

The time courses for the changes in LV pressure, dimension, wall thickness, and meridional wall stress during ejection for a representative subject are shown in Figure 1. LV systolic wall stress peaked early after the onset of ejection, at a time when changes in LV dimension and wall thickness were minimal and LV pressure was increasing. As systole progressed, ventricular dimension decreased and wall thickness increased, resulting in a progressive decrease in wall stress despite little change in pressure.

The hemodynamic response of each of the 10 subjects given dobutamine infusions are shown in Table II. Data are matched for end-systolic pressure. With the dobutamine infusion, heart rate increased by 13% (87 ± 23 versus 98 ± 23 beats/min; $p < 0.05$). For any end-systolic pressure, end-systolic dimension was smaller during the dobutamine infusion than in the absence of the drug. End-diastolic dimension was not significantly affected by the change in inotropic state. The net result was a

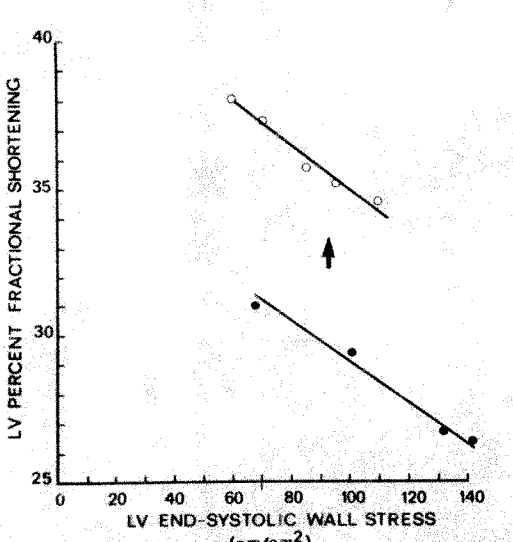

FIGURE 4. Comparison of the LV end-systolic wall stress-shortening lines joining points at different afterloads for control (**closed circles**) and increased (**open circles**) contractile states in a representative subject. With the dobutamine infusion, the % ΔD is higher for any σ_{es}.

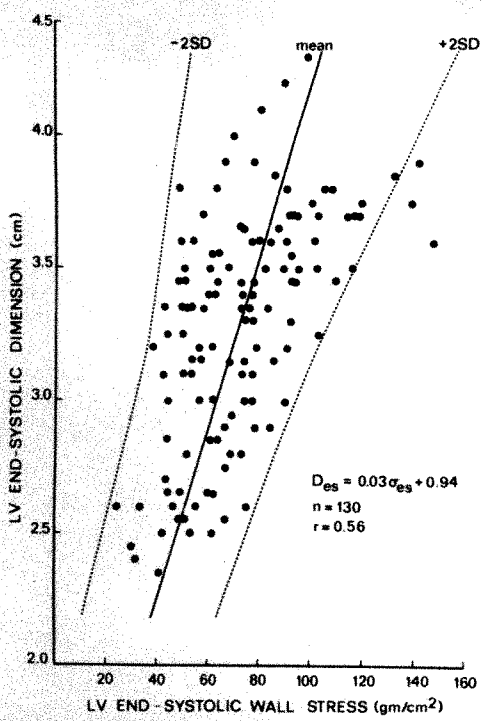

FIGURE 5. Relation between LV end-systolic wall stress (σ_{es}) and dimension (D_{es}) for the 130 control points. Although these variables are linearly related, there is wide scatter, with a correlation coefficient of +0.56.

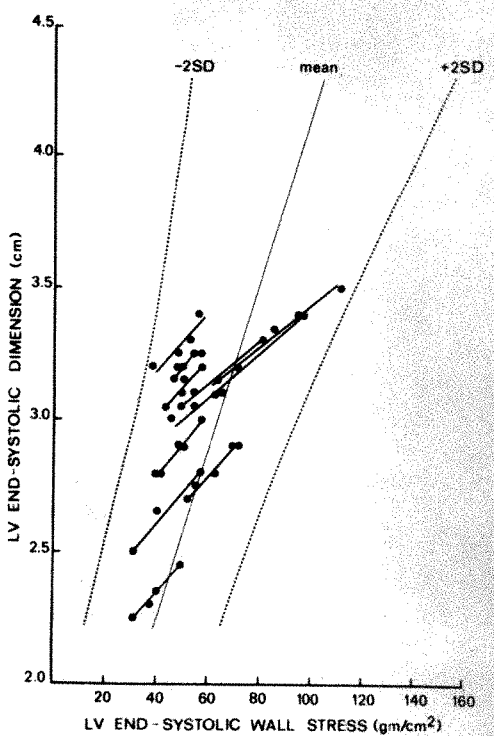

FIGURE 6. Plot of the LV end-systolic wall stress (σ_{es})-dimension (D_{es}) relation. There is extensive overlap between σ_{es}-D_{es} points obtained during dobutamine infusion and the mean ±2 standard deviations for the regression line generated from the 130 control points.

21% mean increase in stroke volume (66 ± 10 to 80 ± 16 ml; $p < 0.01$) and a 38% increase in cardiac output (5.6 ± 1.4 to 7.7 ± 2.2 liters/min; $p < 0.01$).

LV end-systolic stress-shortening relation: When the 130 control points obtained from all 26 patients were pooled, the relation between LV end-systolic stress and shortening was inversely linear with a correlation coefficient of −0.83 (Fig. 2). Using linear regression, percent fractional shortening was best predicted by the following equation: $\%\Delta D = -0.0956(\sigma_{ES}) + 38.7$. With dobutamine infusion, all 43 stress-shortening points were more than 2 standard deviations above the mean values for the regression line (Fig. 3). In each individual case, dobutamine infusion resulted in a higher percent shortening for any end-systolic stress (Table II, Fig. 4). This was demonstrated by the increase in the extrapolated value for shortening when end-systolic stress was zero, from 36.6 ± 2.2 in the absence of dobutamine to 45.5 ± 3.2 ($p < 0.01$) in its presence. The slope of the stress-shortening line did not change consistently with dobutamine, increasing in 8 cases and decreasing in 2.

For individual subjects, an increase in end-systolic stress resulted in small increases in LV mid-wall end-systolic dimension and mid-wall end-diastolic dimension. There was a poor correlation between mid-wall percent fractional shortening and end-systolic wall stress ($r = 0.15$). Sixteen of the 43 dobutamine points fell within the 95% confidence limits for this relation.

LV end-systolic wall stress-dimension relation: The relation between LV end-systolic stress and dimension for the 130 control points showed wide scatter with a correlation coefficient of 0.56 (Fig. 5). Using linear regression, end-systolic dimension was best predicted by the following equation: $D_{ES} = 0.03(\sigma_{ES}) + 0.94$, where D_{ES} is end-systolic dimension and σ_{ES} is end-systolic wall stress. Unlike the situation with the stress-shortening relation, the 43 stress-dimension points obtained during the dobutamine infusion fell within the range of the 130 pooled control points (Fig. 6). When the stress-dimension relation was analyzed for individual subjects, the curves were linear under control ($r \geq 0.91$) and increased inotropic states ($r \geq 0.92$). During the dobutamine infusion, the lines joining stress-dimension points at different afterloads were uniformly shifted to the right, resulting in smaller values of end-systolic dimension for any end-systolic stress. This is illustrated for a representative subject in Figure 7. For the 10 subjects who received dobutamine, the extrapolated end-systolic dimension value when stress was zero was consistently smaller with the positive inotropic intervention (2.8 ± 0.1 versus 2.4 ± 0.3; $p < 0.05$).

When each subject was used as his own control, the relative position, but not the slope, of the stress-dimension relation was sensitive to inotropic state. The relation between wall stress and chamber dimension changed throughout ventricular ejection (Fig. 8). Nei-

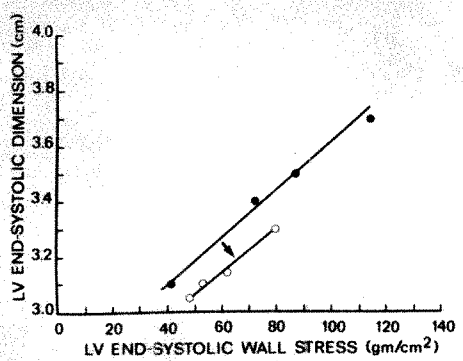

FIGURE 7. Comparison of the LV end-systolic wall stress-dimension lines joining points at different afterloads for control (**closed circles**) and increased (**open circles**) inotropic states in a representative subject. The end-systolic dimension was smaller during dobutamine infusion than under control conditions, despite comparable values for end-systolic wall stress.

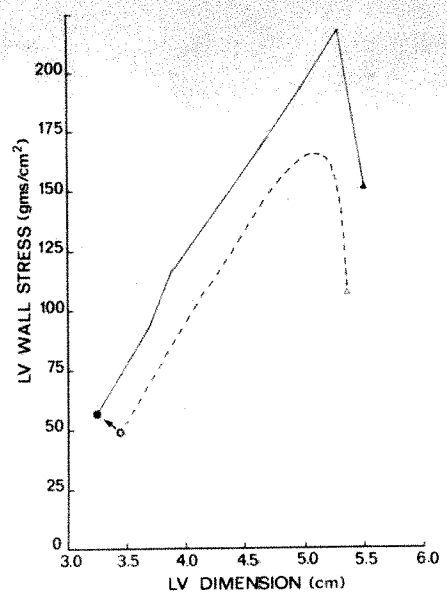

FIGURE 8. Comparison of the LV wall stress (σ)-dimension (D) plot for control (**dashed lines**) and increased inotropic (**solid line**) conditions in a representative subject. Neither the σ-D relation at onset of ejection (**triangles**) nor its course during ventricular shortening was able to distinguish between different inotropic states. LV ventricular end-systolic dimension (**circles**) was smaller during dobutamine infusion than under control conditions despite comparable values for end-systolic wall stress.

ther the stress-dimension relation in early systole nor its course during ventricular ejection was able to distinguish between different inotropic states. However, changes in contractility affected the position of the end-systolic stress-length relation.

Discussion

Methodologic considerations: Our study analyzed multiple points in each subject under both control and altered inotropic conditions in an effort to study LV function at end-systole. Rather than extrapolating conclusions from data generated by a single or at most 2 postextrasystolic potentiated beats, as has been the usual practice,[11,22,25] we analyzed the significance of position, slope, and axis intercept for the end-systolic stress-shortening and stress-dimension relations over a wide range of afterload conditions. This was accomplished using a safe, easily performed experimental design that requires minimal patient cooperation.

Certain potential limitations to this study should be noted. First, we used meridional wall stress rather than circumferential wall stress as a measure of LV afterload at end-systole. LV meridional stress, which is dependent only on ventricular intracavitary pressure, wall thickness, and diameter in the equatorial plane, can be calculated accurately using noninvasive techniques.[24] Although absolute values for meridional stress are lower than absolute values for circumferential stress because of differences in the radii of curvature in meridional and circumferential planes,[26] numerous studies have demonstrated that both variables are related to ventricular performance.[23,26,27]

Second, left ventricular percent fractional shortening is dependent on preload, afterload, and contractile state. In our study, contractility was assessed during primary alterations in LV afterload. Since preload has relatively little effect on the extent of ventricular shortening in patients without volume overload,[28] the relation between LV extent of shortening and force resisting shortening at end-systole (that is, wall stress), should reflect intrinsic contractile state. The possibility that an "afterload mismatch" occurred resulting in a depressed fractional shortening value out of proportion to end-systolic stress is unlikely since there was no limit to preload reserve as demonstrated by maintenance of a constant LV stroke volume despite increases in afterload.[4,29]

Third, the use of M-mode echocardiography in determining representative LV minor axis dimensions assumes symmetrical wall motion. While this assumption may be supported in normal subjects as well as in patients with valvular and diffuse myopathic diseases, this technique may be inaccurate in patients with coronary artery disease in whom regional wall motion may

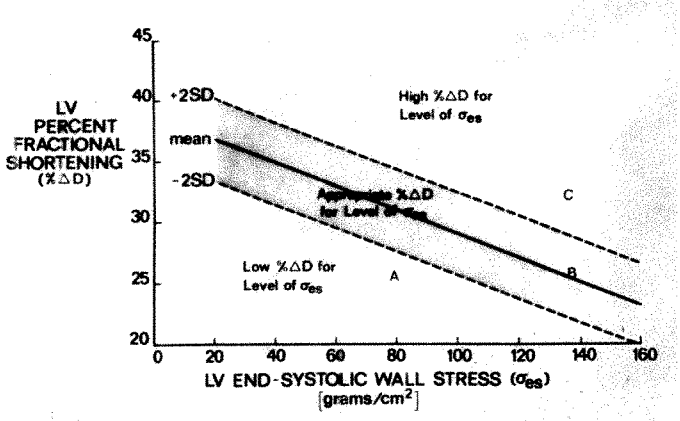

FIGURE 9. Diagram of the LV end-systolic wall stress (σ_{es})-shortening (% ΔD) relation. This relation may be useful in distinguishing depressed myocardial shortening due to excessive afterload (point B) from intrinsic contractile abnormality (point A). Hypercontractile states would be characterized by a higher than predicted % ΔD for any σ_{es} (point C versus point B).

not be representative of global LV performance. Two-dimensional echocardiography may be helpful in determining how any given diameter determined by M-mode echocardiography reflects the performance of the ventricle as a whole. The reproducibility of echocardiographic measurements of LV dimension is important to the validity of our results. We attempted to minimize this potential problem by recording all measurements over a short period (<30 minutes), using 1 technician, keeping the patient and transducer positions stationary throughout the study, and employing the guidelines for echocardiographic measurements recommended by the American Society for Echocardiography.[30] A recent study using a similar approach found no statistically significant intra- or interobserver variation in M-mode echocardiographic measurement of end-systolic or end-diastolic dimension in normal subjects studied serially over a 4 week period.[31]

Fourth, we assumed that ventricular contractile state remained uniform under increased afterloading conditions. Although methoxamine has no direct cardiac inotropic effect,[14,15] the possibility of sympathetically mediated reflex changes in contractility cannot be excluded. However, this possibility appears unlikely, since heart rate remained relatively constant as afterload was altered. In addition, sympathetically mediated reflexes have, at most, a small contribution to the resting inotropic state in normal human subjects.[32,33] This was confirmed recently by Crawford et al,[34] who studied the cardiac effects of an acute pressure load in normal subjects after administration of atropine and atropine plus propranolol. No significant difference in ventricular performance was observed before or during beta-blockade therapy, suggesting that the sympathetic nervous system has minimal influence on the heart during an acute afterload challenge.

Finally, we used the pressure at end-ejection to approximate true end-systolic pressure. While the aortic incisural pressure may slightly underestimate LV pressure at the instant of maximal ventricular active contraction, the difference between these 2 points is probably small.[35] Although some investigators have used *peak* systolic pressure to approximate true end-systolic pressure, we recently showed that the end-systolic pressure-dimension relation using incisural rather than peak systolic pressure is more sensitive to alterations in ventricular contractility, especially in patients with high cardiac output states.[12]

Implications: The primary findings of this study are that LV end-systolic wall stress and percent fractional shortening are inversely and linearly related, that this relation is highly sensitive to alterations in inotropic state, and that this relation can be accurately assessed by noninvasive methods. The LV end-systolic stress-dimension relation, while less sensitive in assessing the baseline LV inotropic state, nevertheless can be used to detect whether an intervention alters this state.

As may be noted in Figure 1, LV wall stress is normally highest early during ventricular systole and then declines throughout the remainder of the ejection period. In the normal heart, the decline in ventricular dimension and the increase in wall thickness that occur after aortic valve opening are responsible for this decline, which occurs despite the increase in intracavitary pressure during most of the ejection period.[23] LV wall stress at end-systole represents the force (afterload) which the shortened myocardial fibers cannot overcome. At this point, the active and isovolumetric force-length relations become equal, the active state ends, and ventricular shortening is terminated.[7,8] Our results indicate that the greater the load opposing shortening at end-systole, the smaller the extent of shortening. The significance of this interaction should be emphasized. As shown in Figure 2, a fractional shortening of 30% would be well within the normal range if end-systolic stress were 80 g/cm^2, but abnormally depressed if end-systolic stress were 40 g/cm^2. Thus, for the percent fractional shortening (or any other ejection phase index of LV performance) to reflect the intrinsic contractile state accurately, it must be defined in terms of the force at the termination of ejection. This study presents the range of values for the end-systolic stress-shortening relation in normal human subjects. It is of interest that mid-wall percent fractional shortening did not show a similar inverse correlation with increasing end-systolic wall stress, as was seen with internal dimension percent fractional shortening. This probably reflects the fact that mid-wall percent fractional shortening is not equivalent to mid-wall fiber shortening, since wall thickness (used in the calculation of mid-wall percent fractional shortening) changes markedly from end-diastole to end-systole. In contrast, internal dimension percent fractional shortening probably does reflect accurately the extent of myocardial fiber shortening.

The findings with the infusion of dobutamine, a beta-adrenergic agonist, illustrate how the end-systolic stress-shortening relation reflects changes in contractile state. For any end-systolic stress, the extent of myocardial fiber shortening was greater with the positive inotropic intervention than under control conditions (Fig. 3). The results of the dobutamine infusion also illustrate the concept of LV systolic reserve capacity. In each case, the dobutamine infusion resulted in a smaller end-systolic dimension for any end-systolic pressure despite a relatively constant end-diastolic dimension. This resulted in a rightward shift of the end-systolic stress-dimension relation as well as increases in LV percent fractional shortening and stroke volume.

The end-systolic stress-shortening plot for normal subjects obtained over a wide range of afterload conditions may be used in patients with reduced ejection phase indexes of LV performance to distinguish reduced myocardial shortening due to excessive afterload from depressed myocardial contractility (Fig. 9). Since force is expressed as end-systolic wall stress, which takes into account both LV chamber size and wall thickness, it should be possible to compare stress-shortening and stress-dimension relations in patients of different sizes and ages. In patients at risk for LV dysfunction, such as those with systemic hypertension and cardiomyopathy, a normal fractional shortening at a low end-sys-

tolic stress may represent a subtle preclinical abnormality in LV inotropic state not evident from other cardiac studies. This method may be of value in following asymptomatic patients with valvular heart disease, in whom deterioration of myocardial contractility often precedes the development of symptoms, and may point to the desirability of early surgical intervention. The applicability of this approach in patients with LV outflow tract obstruction needs to be investigated. Finally, this noninvasive technique may be useful in assessing the effects of potentially cardiotoxic drugs such as Adriamycin® on LV contractility,[36] and in assessing the effects on contractile state of drugs having purported positive inotropic effects, such as orally active sympathomimetic agents.

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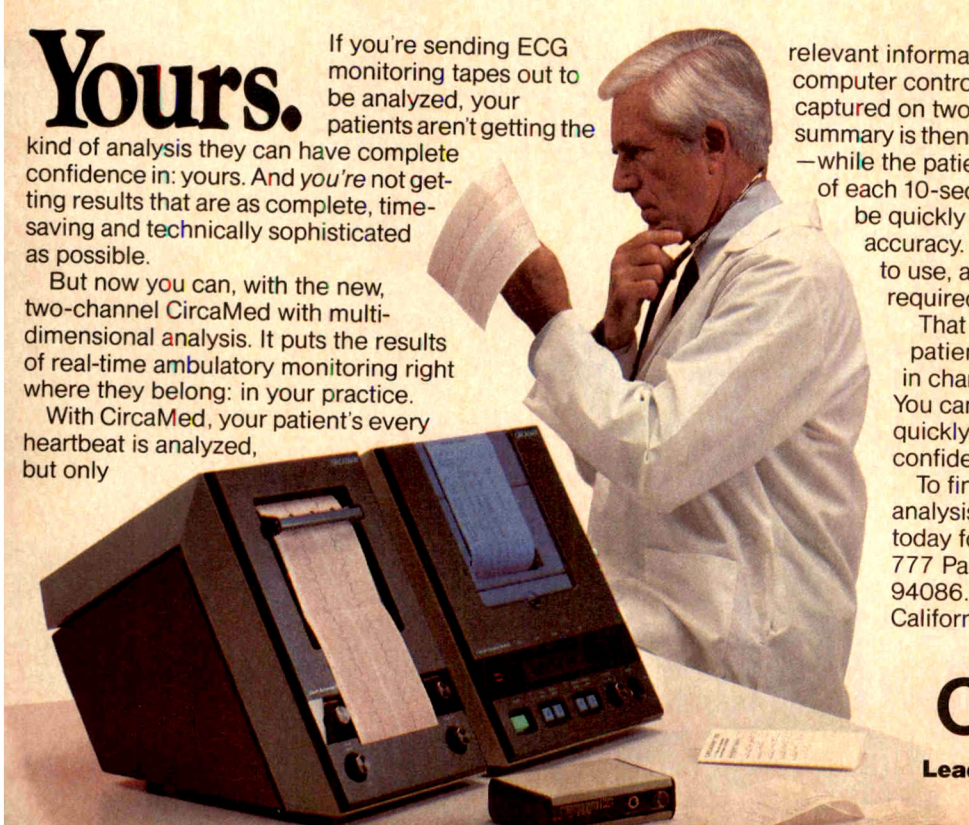

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Reference: 1. AMA Department of Drugs: AMA Drug Evaluations, ed. 4. Littleton, Mass., Publishing Sciences Group, Inc., 1980, p. 520.

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BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

CONTRAINDICATIONS

1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless it is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: In congestive heart failure, inhibition with beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In patients already receiving digitalis, propranolol may reduce the positive inotropic action of digitalis and may have an additive depressant effect on AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, in rare instances, cardiac failure has developed during propranolol therapy. At the first sign of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and observed closely. a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Give special consideration to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol should be withdrawn slowly, since abrupt withdrawal may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta-blockade impairs the ability of the heart to respond to reflex stimuli. Except in pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery. In case of emergency surgery, the effects of propranolol can be reversed by administration of beta-receptor agonists such as isoproterenol or levarterenol, but such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), administer with caution, since propranolol may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in patients with labile diabetes. A precipitous elevation of blood pressure may accompany hypoglycemic attacks.

USE IN PREGNANCY: Safe use in human pregnancy not established. Embryotoxic effects have been seen in animals at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if propranolol is administered, since it may occasionally produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

Observe laboratory parameters at regular intervals. Use with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta-blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

HOW SUPPLIED

TABLETS

—Each hexagonal-shaped, orange, scored tablet is embossed with an "I" and imprinted with "INDERAL 10," contains 10 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0421-81) and 1,000 (NDC 0046-0421-91). Also in unit dose package of 100 (NDC 0046-0421-99).

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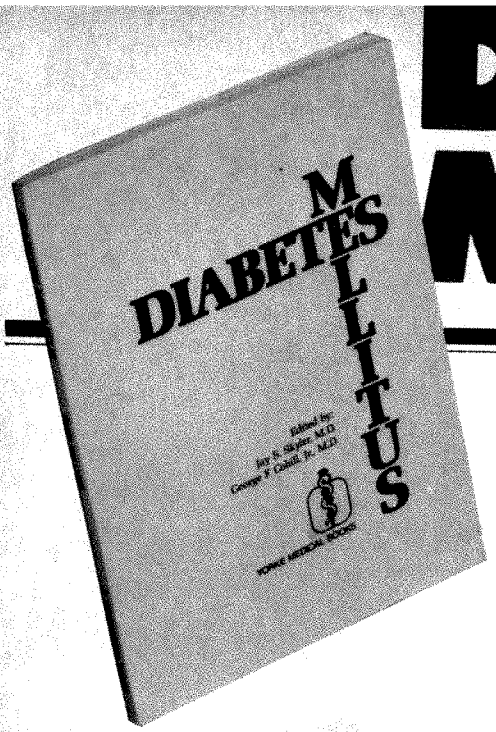

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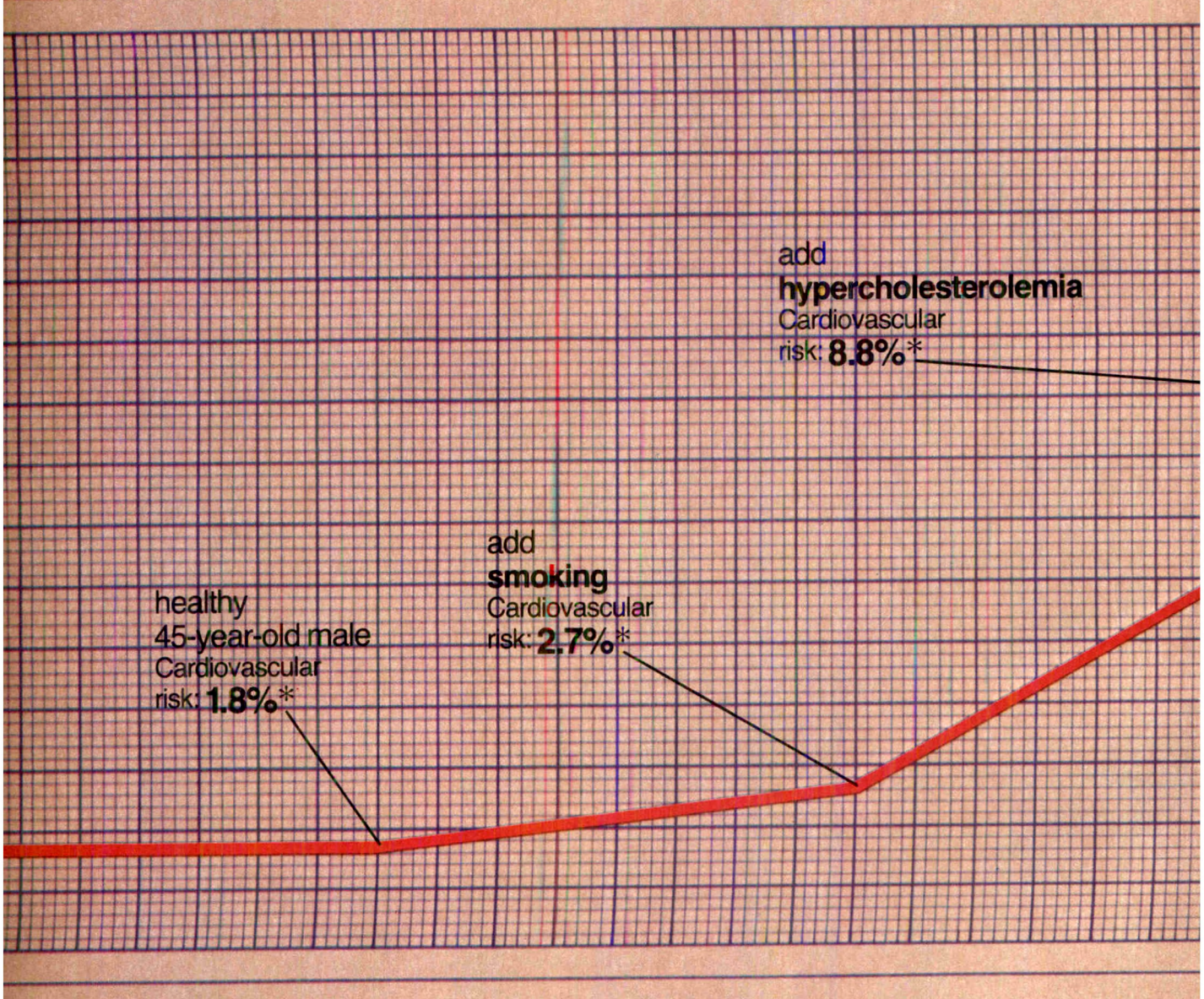
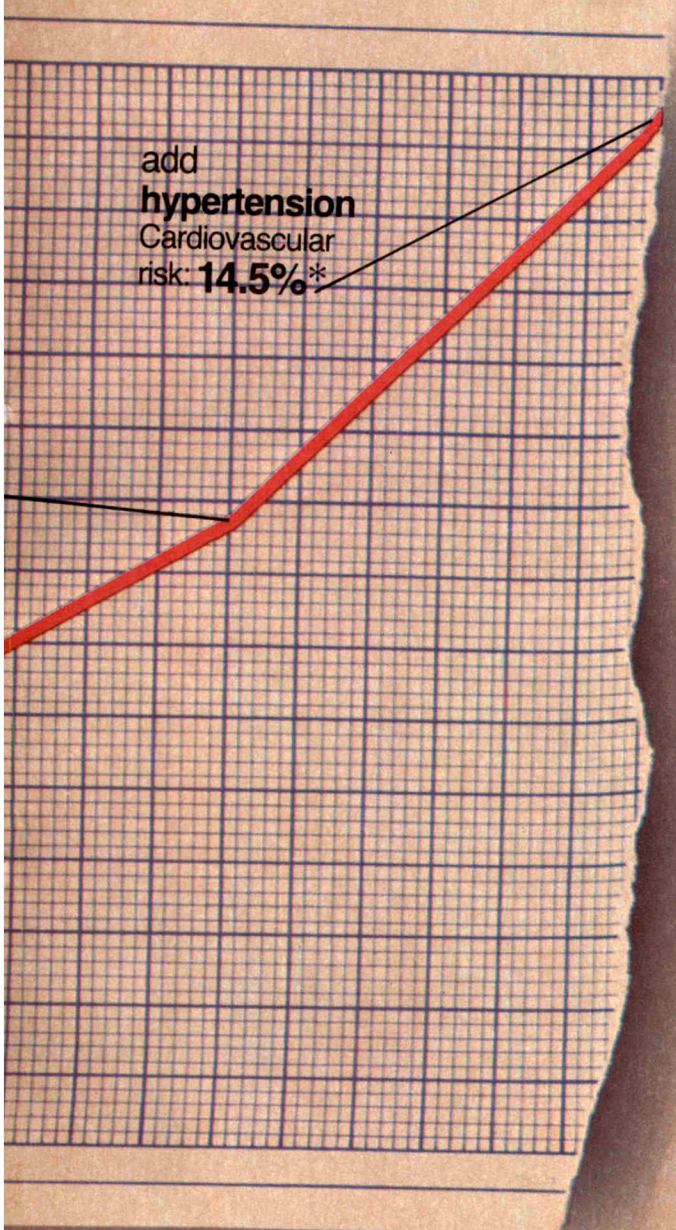


Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

*Percent equals chances in 100 of developing coronary heart disease within 6 years.

Adapted from *Coronary Risk Handbook:* Estimating risk of coronary heart disease in daily practice. 1973, American Heart Assoc., Inc.

Consider the Risks



▪ When selecting antihypertensive therapy, clinical consideration should be given to the effects of the specific drug on coronary risk factors. Blood pressure control should be achieved without adversely affecting blood lipids.

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†Minipress is not indicated for the treatment of hyperlipidemia.

Please see Minipress brief summary on following page.

Minipress®
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Capsules 1 mg, 2 mg, 5 mg

BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*
INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.
WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.
If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.
Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.
More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.
Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.
ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.
The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established.)
Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.
Cardiovascular: edema, dyspnea, syncope, tachycardia.
Central Nervous System: nervousness, vertigo, depression, paresthesia.
Dermatologic: rash, pruritus, alopecia, lichen planus.
Genitourinary: urinary frequency, incontinence, impotence, priapism.
EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.
Other: diaphoresis.
Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.
In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.
DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:
Initial Dose: 1 mg two or three times a day (See Warnings.)
Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.
Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.
HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).
More detailed information available on request.

References: 1. O'Conner DJ, Preston RA, Sasso EH: Renal perfusion changes during treatment of essential hypertension: Prazosin versus propranolol. *J Cardiovasc Pharmacol* 1(suppl):S38-S42, 1979. 2. Falase AO, Salako LA: The effect of prazosin combined with a diuretic, polythiazide, in hypertensive Africans. *Curr Ther Res* 25:10-15, 1979. 3. Okun R, Maxwell M: Long-term antihypertensive therapy with prazosin plus a diuretic. *J Cardiovasc Pharmacol* 1(suppl):S21-S27, 1979. 4. Kirkendall WM, Hammond JJ, Thomas JC, et al: Prazosin and clonidine for moderately severe hypertension. *JAMA* 240 (23): 2553-2556, December 1, 1978. 5. Harter HR, Delmez JA: Effects of prazosin in the control of blood pressure in hypertensive dialysis patients. *J Cardiovasc Pharmacol* 1(suppl):S43-S55, 1979. 6. Leren P, Foss PO, Helgeland A, et al: Effect of propranolol and prazosin on blood lipids: The Oslo study. *Lancet*: 4-6, July 5, 1980. 7. Lowenstein J, Neusy A-J: The biochemical effects of antihypertensive agents and the impact on atherosclerosis. *J Cardiovasc Pharmacol* 4 (suppl 2):S262-S264, 1982. 8. Kokubu T, Itoh I, Kurita H, et al: Effect of prazosin on serum lipids. *J Cardiovasc Pharmacol* 4 (suppl 2):S228-S232, 1982. 9. Velasco M, Silva H, Morillo J, et al: Effect of prazosin on blood lipids and on thyroid function in hypertensive patients. *J Cardiovasc Pharmacol* 4 (suppl 2):S225-S227, 1982.

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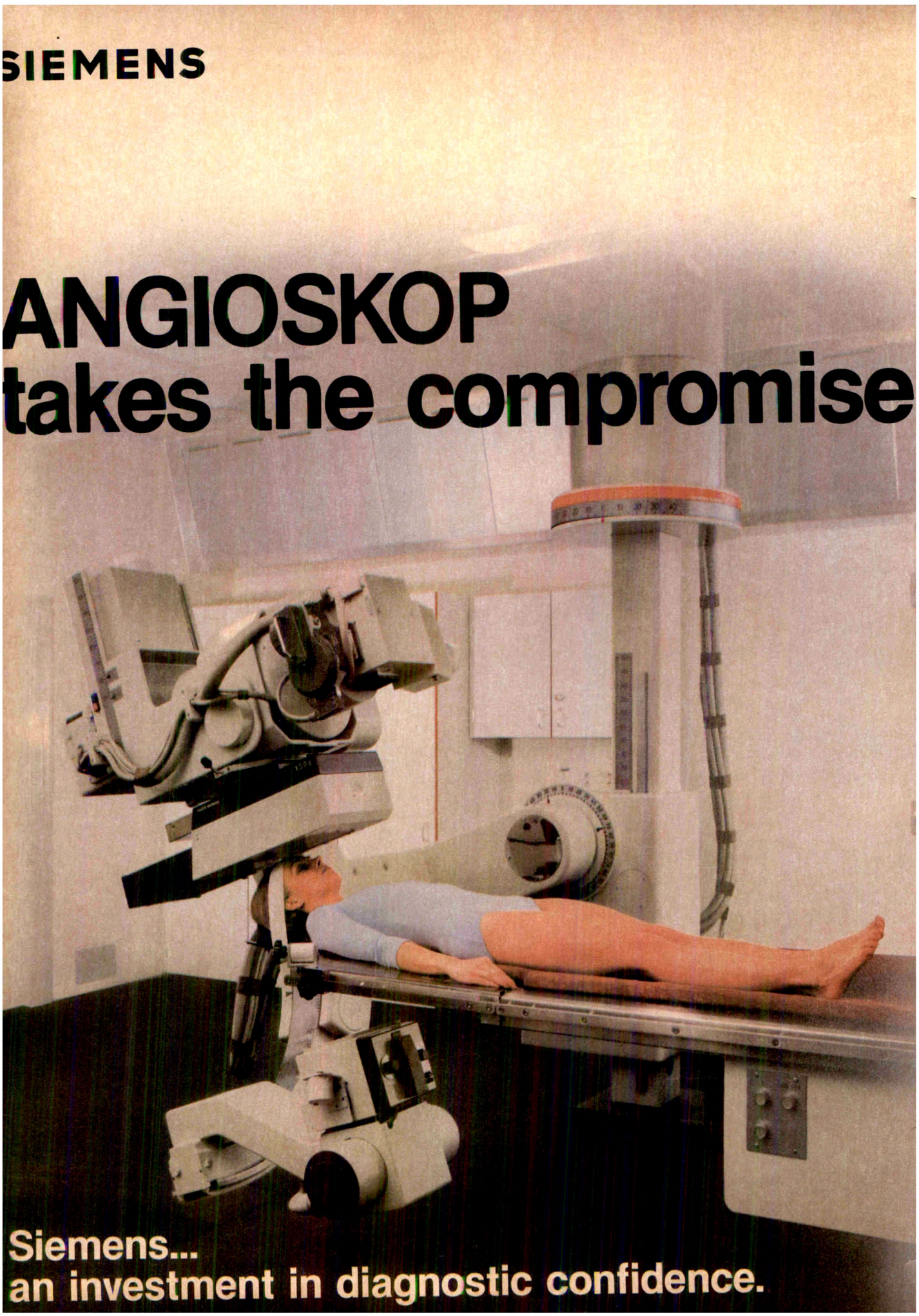

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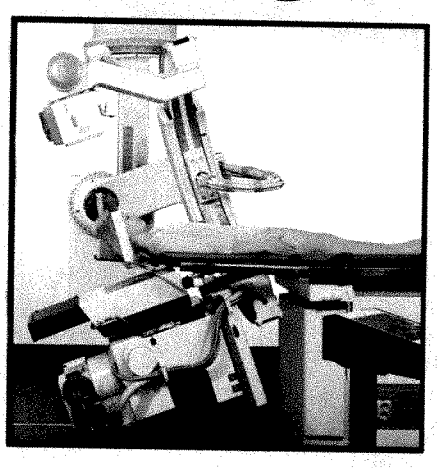

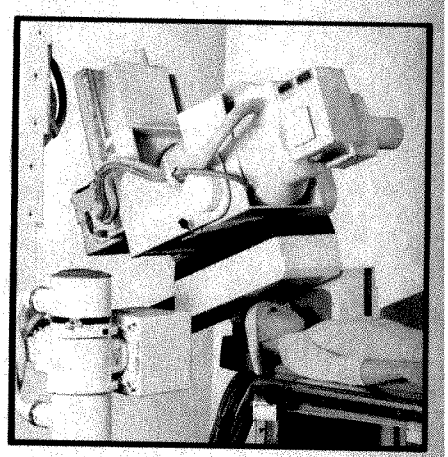

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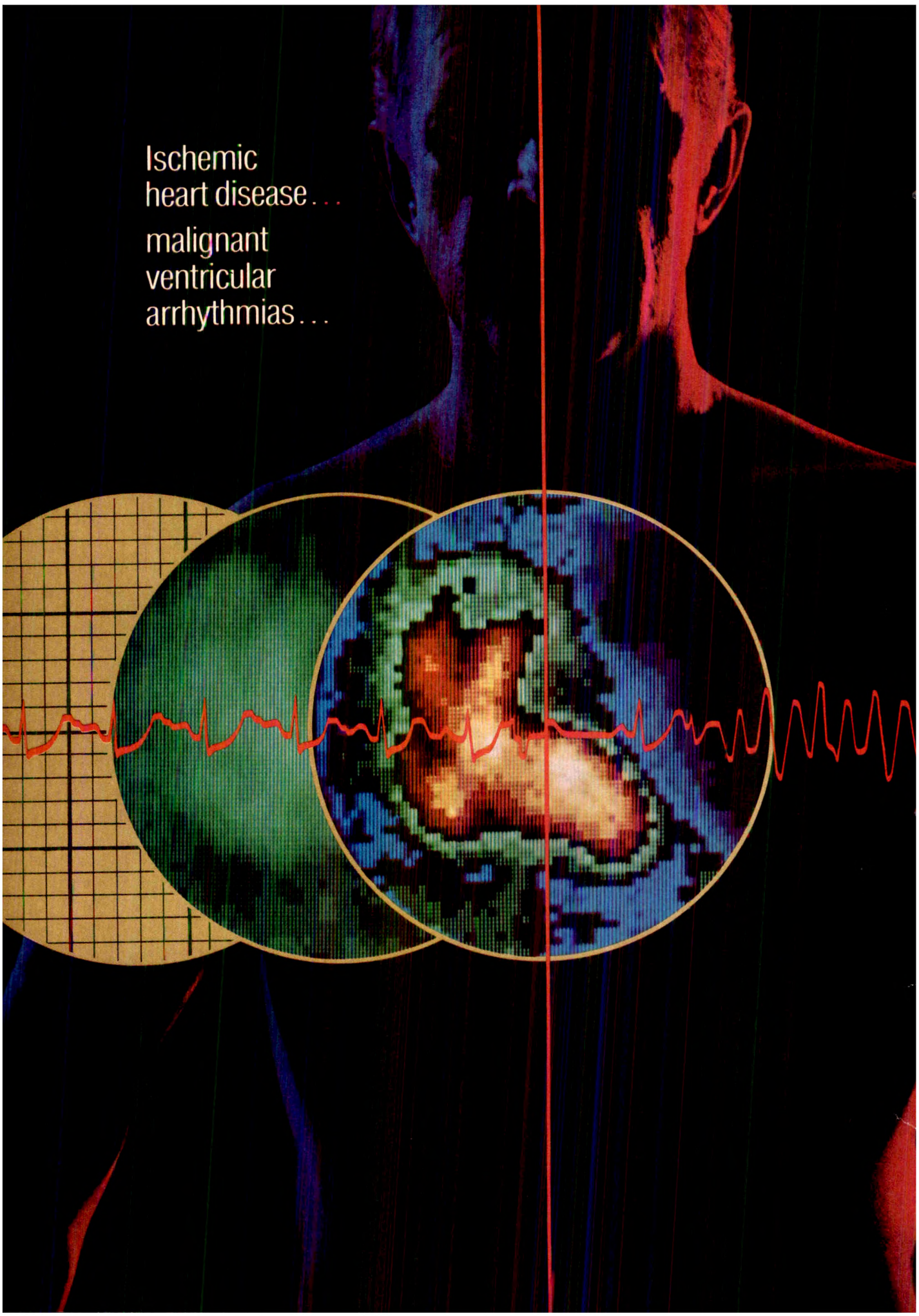
Ischemic
heart disease...
malignant
ventricular
arrhythmias...

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Frequent and complex forms of PVCs sharply increase the risk of sudden cardiac death (SCD) in patients with ischemic heart disease, especially in the presence of left ventricular dysfunction.[1,2]

To reduce the risk of potentially fatal arrhythmias in such patients

QUINAGLUTE® 324 mg DURA-TABS®

(quinidine gluconate)

- If initially tolerated, can usually be taken successfully over long periods.[3]
- Demonstrated by programmed ventricular stimulation to be effective in accepted "standard" doses.[4]
- BID or TID dosage helps improve compliance while providing 24-hour antiarrhythmic activity.
- "As a rule, GI toxicity associated with quinidine gluconate is less frequent and less severe than that associated with quinidine sulfate."[5]

References: **1.** Lown B, Podrid PJ, Graboys TB, et al: *Curr Probl Cardiol* 4:13-14, 1980. **2.** Schulze RA Jr, Strauss HW, Pitt B: *Am J Med* 62:192-199, 1977. **3.** Pine MB, Aronow WS: *Ration Drug Ther* 14:1-5, 1980. **4.** Kastor JA, Horowitz LN, Harken AH, et al: *N Engl J Med* 304: 1004-1020, 1981. **5.** Podrid PJ: *Patient Care* 15:100-132, 1981.

Please turn page for brief summary of prescribing information.

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QUINAGLUTE® (quinidine gluconate) DURA-TABS®

INDICATIONS AND USAGE: Quinaglute (quinidine gluconate) Dura-Tabs are indicated in the prevention and/or treatment of:

1. Ventricular arrhythmias: Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock). **2. Junctional (nodal) arrhythmias:** A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).

CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.

WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine. 2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered. 3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring. 4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals. 5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity. 7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal. 8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.

Drug Interactions:

Drug	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers: Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.

Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.

ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea. Less frequently encountered adverse reactions:

Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.

Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.

Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.

Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.

Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.

See package insert for full information.

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Please see reverse side for
brief summary of prescribing information.

TYLENOL® with Codeine ©

(acetaminophen with codeine)

TABLETS and CAPSULES:
acetaminophen 300 mg plus codeine phosphate:
No. 3—30 mg (½ gr); No. 4—60 mg (1 gr)

Summary of Prescribing Information

Description

Tablets: Contain codeine phosphate*: No. 1—7.5 mg (⅛ gr); No. 2—15 mg (¼ gr); No. 3—30 mg (½ gr); No. 4—60 mg (1 gr)—plus acetaminophen 300 mg.

Capsules: Contain codeine phosphate*: No. 3—30 mg (½ gr); No. 4—60 mg (1 gr)—plus acetaminophen 300 mg.

Elixir: Each 5 ml contains 12 mg codeine phosphate* plus 120 mg acetaminophen (alcohol 7%).

***Warning:** May be habit forming.

Actions: Acetaminophen is an analgesic and antipyretic; codeine an analgesic and antitussive.

Contraindications: Hypersensitivity to acetaminophen or codeine.

Warnings: *Drug dependence:* Codeine can produce drug dependence of the morphine type and may be abused. Dependence and tolerance may develop upon repeated administration; prescribe and administer with same caution appropriate to other oral narcotics. Subject to the Federal Controlled Substances Act.

Usage in ambulatory patients: Caution patients that codeine may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

Interaction with other CNS depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) with this drug may exhibit additive CNS depression. When such a combination is contemplated, reduce the dose of one or both agents.

Usage in pregnancy: Safe use not established. Should not be used in pregnant women unless potential benefits outweigh possible hazards.

Pediatric use: Safe dosage of this combination has not been established in children below the age of three.

Precautions: *Head injury and increased intracranial pressure:* Respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: Codeine or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.

Special risk patients: Administer with caution to certain patients such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Adverse Reactions: Most frequent: lightheadedness, dizziness, sedation, nausea and vomiting, more prominent in ambulatory than in nonambulatory patients; some of these reactions may be alleviated if the patient lies down. Others: euphoria, dysphoria, constipation and pruritus.

Dosage and Administration: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. TYLENOL with Codeine tablets and capsules are given orally. The usual adult dose is: Tablets No. 1, No. 2, and No. 3 and capsules No. 3: One or two every four hours as required. Tablets and capsules No. 4: One every four hours as required. TYLENOL with Codeine elixir is given orally. The usual doses are **Children (3 to 6 years):** 1 teaspoonful (5 ml) 3 or 4 times daily; **(7 to 12 years):** 2 teaspoonsful (10 ml) 3 or 4 times daily; **(under 3 years):** safe dosage has not been established. **Adults:** 1 tablespoonful (15 ml) every 4 hours as needed.

Drug Interactions: CNS depressant effect may be additive with that of other CNS depressants. See Warnings.

For information on symptoms/treatment of overdosage, see full prescribing information.

Full directions for use should be read before administering or prescribing.

TYLENOL with Codeine tablets and capsules are manufactured by McNeil Pharmaceutical Co., Dorado, Puerto Rico 00646.

Caution: Federal law prohibits dispensing without prescription.

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Electrophysiologic Testing in the Evaluation of Patients With Syncope of Undetermined Origin

DAVID S. HESS, MD, FRED MORADY, MD, and MELVIN M. SCHEINMAN, MD

Thirty-two patients were prospectively evaluated for syncope (recurrent in 26 patients) with conventional neurologic and cardiovascular testing without elucidation of a cause. All patients underwent invasive electrophysiologic studies to assess sinus nodal function, atrioventricular conduction, and the inducibility of supraventricular and ventricular tachycardia (VT). Eleven patients (34%) were found to have laboratory-induced VT, 5 patients (15%) had evidence of sinus nodal dysfunction, 1 patient (3%) had infra-His atrioventricular block during atrial pacing, and 1 patient (3%) had probable quinidine-related VT. The remaining 14 patients had no detectable abnormalities during electrophysiologic study. After a mean follow-up period of 21.3 ± 1.2 months, 10 of the 11 patients with inducible VT were asymptomatic while receiving laboratory-directed antiarrhythmic therapy, and 1 patient died from ventricular fibrillation after discontinuing the chosen antiarrhythmic regimen. Five of the remaining 7 patients with an electrophysiologic abnormality were asymptomatic after implantation of a permanent pacemaker or alteration of previous drug therapy, or both. The 14 patients with a normal electrophysiologic study were treated empirically, with recurrent syncope occurring in 4 of these patients during the follow-up period. Invasive electrophysiologic studies provided a presumptive diagnosis in 56% of patients with syncope of undetermined origin. Previously unsuspected VT accounted for 61% (11 of 18) of the detected abnormalities. Therapy specific for the electrophysiologic abnormality was usually successful in preventing recurrent syncope.

Since Scherlag et al[1] first recorded the His bundle potential in man in 1969, invasive electrophysiologic techniques have been employed in a variety of clinical settings to evaluate cardiac impulse formation and conduction. Although these invasive methods were initially limited to the assessment of sinus nodal function and atrioventricular conduction,[2,3] recent studies have demonstrated that spontaneously occurring supraventricular and ventricular arrhythmias can be reliably reproduced in the electrophysiology laboratory.[4–9] This ability to provoke clinical tachyarrhythmias has also provided the foundation for the laboratory assessment of antiarrhythmic therapy.[10–15]

Several published studies have evaluated sinus node function and atrioventricular conduction in patients with syncope.[16,17] These studies were primarily designed to detect occult bradyarrhythmias and were not employed to provoke tachyarrhythmias. The present study was undertaken to assess the value of comprehensive invasive electrophysiologic techniques in patients with syncope but no discernible cause after thorough medical and neurologic evaluation. The study was designed to detect both bradyarrhythmias and previously unsuspected supraventricular and ventricular tachyarrhythmias with invasive electrophysiologic methods.

From the Department of Medicine, Division of Cardiology, University of California, San Francisco, California. Manuscript received March 2, 1982; revised manuscript received June 7, 1982, accepted June 16, 1982.

Address for reprints: David S. Hess, MD, Division of Cardiovascular Medicine and Surgery, Memorial Medical Center, 3625 University Boulevard South, Jacksonville, Florida 32216.

Methods

Clinical evaluation and characteristics: Thirty-two patients with syncope referred to the Cardiology Service of the University of California Medical Center from January 1, 1979 to October 1, 1980 were evaluated with conventional medical and neurologic techniques. Syncope was defined as a clinical syndrome characterized by abrupt, transient loss of consciousness with inability to maintain postural tone. All patients underwent a complete medical history, physical examination, and routine laboratory testing. Postural vital signs were recorded in all patients, and individual right and left carotid sinus massage was performed during continuous electrocardiographic (ECG) monitoring. The history was reviewed with special emphasis on the situation and environment at the time of syncope, and, when possible, witnesses to the episode were interviewed. Neurologic consultation was

obtained in all patients. Eighteen patients had both brain imaging (15 by computerized tomography, 1 by radionuclide technique, and 2 by angiography) and electroencephalography. Five patients had only electroencephalograms and 2 had only computerized tomography. At the recommendation of the consulting neurologist, 7 patients had neither procedure performed. Patients had an average of 49.5 ± 5.7 hours of coronary care unit monitoring and 52.0 ± 4.0 hours of ambulatory ECG monitoring. Exercise treadmill testing was carried out if the syncope was related to exertion or associated with chest pain. Left ventricular function was assessed with either M-mode and 2-dimensional echocardiography, gated radionuclide wall motion study, or cardiac catheterization.

There was no evidence of seizure disorder, supraventricular or ventricular tachycardia, bradyarrhythmia (heart rate <45 beats/min), postural hypotension, carotid sinus hypersensitivity, or fixed obstructive valvular heart disease in any patient. During the periods of continuous ECG monitoring, no patient had >30 premature ventricular depolarizations/hour or runs of ≥3 consecutive premature ventricular depolarizations.

The clinical characteristics of the 32 patients (22 men and 10 women) are outlined in Table I. The patients ranged in age from 28 to 87 years (mean 60.2 ± 3.4) and had had 1 to 10 syncopal episodes (mean 3.8 ± 0.5) over an average period of 19.6 ± 5.0 months. Six patients had had only 1 syncopal episode but in 5 of these cases significant morbidity had been associated with the syncope (automobile accident in 2 patients, fractured hip in 1 patient, cerebral concussion in 1 patient, and basilar skull fracture in 1 patient). These patients were entered into the study on a compassionate basis when the conventional evaluation failed to determine a cause.

Five patients had a history of mild to moderate hypertension (1 with congestive heart failure), 7 patients had atherosclerotic coronary artery disease (1 with congestive heart failure), and there was 1 patient each with mitral valve prolapse, systemic sarcoidosis, hypertrophic obstructive cardiomyopathy, rheumatic mitral regurgitation, and congestive cardiomyopathy. Fifteen patients had no underlying organic heart disease.

The initial electrocardiogram demonstrated left bundle branch block in 3 patients, right bundle branch block with left anterior hemiblock in 3 patients, and right bundle branch block with left posterior hemiblock in 1 patient. Six patients had left ventricular hypertrophy and 3 patients had evidence of old myocardial infarction. Six patients had been taking digoxin, 6 patients quinidine, and 3 patients propranolol at the time of the last recorded syncopal episode.

TABLE I

Patient	Age (yr) & Sex	Syncopal Episodes	Duration of Symptoms (mo)	Clinical Heart Disease	ECG	HQ (ms)	Electrophysiologic Findings	Treatment	Follow-Up (mo)	Symptoms
1	28M	2	17	HOCM	LVH	76	VT; CL = 260	Q, T, PR	30	None
2	87M	8	48	None	NL	40	VT; CL = 180	P, A	16	None
3	67M	8	24	RHD	LVH	90	VT; CL = 270	D, P	16	None
4	51M	2	6	CAD	MI	42	VT; CL = 325	D, P	32	None
5	40M	4	2	MVP	NL	50	VT; CL = 170	PR	19	None
6	64M	1	1	CAD	LBBB	80	VT; CL = 160	P, PACE	19	None
7	76M	2	1	CAD	RB + LPHB	85	VT; CL = 200	P, A, PACE	16	None
8	60M	1	1	CM	RB + LAHB	70	VT; CL = 200*	P, PACE	6	Died, VF
9	70M	1	1	HTN	LVH	70	VT; CL = 350*	P, PACE	16	None
10	81F	4	12	HTN	LVH	50	VT; CL = 230*	Q	21	None
11	78M	1	1	None	NL	60	VT; CL = 180*	P	16	None
12	30M	4	12	CAD	LVH	45	SA ENT block	D/C PR	32	None
13	74F	7	60	None	NL	40	SA ENT block	PACE	20	Syncope, 9 mo
14	39M	2	96	None	NL	40	2° pauses†	None	17	None
15	87M	1	1	None	RB + LAHB	50	SACT = 274 ms	PACE	17	None
16	29F	6	6	None	NL	40	SACT = 260 ms	D	17	Syncope, 2 mo
17	67M	2	1	CAD	RB + LAHB	60	Mobitz II	PACE	34	None
18	69M	1	1	CAD	LBBB	70	Q-related VT	D/C Q, PACE	5	Died, MI
19	58F	3	36	CAD	MI	50	NL	P	16	None
20	78F	4	12	HTN	LAD	35	NL	D/C Q	36	None
21	34M	2	12	None	NL	40	NL	None	32	None
22	39M	10	120	None	NL	30	NL	None	17	Syncope, 4 mo
23	34F	10	8	None	NL	46	NL	P, PH, PB	30	Syncope, 5 mo
24	40M	8	36	None	NL	40	NL	PR, PH, PACE	20	Syncope, 6 mo
25	84F	8	12	None	NL	42	NL	ASA	24	None
26	73F	4	12	None	NL	35	NL	PACE	19	Syncope, 12 mo
27	60M	2	6	None	NL	80	NL	D/C Q	27	None
28	72F	2	12	HTN	LVH	40	NL	PACE	20	None
29	73M	2	15	None	NL	40	NL	P	24	None
30	69F	2	2	None	LAHB	50	NL	Diet‡	25	None
31	83M	2	48	HTN	A FIB	45	NL	D/C Q	19	None
32	33M	4	4	SARC	LBBB	75	NL	PACE	20	None
Mean	60.2	3.8	19.6			53.6			21.3	
SEM	± 3.4	± 0.5	± 5.0			± 3.0			± 1.2	

A = amiodarone; A FIB = atrial fibrillation; ASA = aspirin; CAD = coronary artery disease; CL = cycle length; CM = cardiomyopathy; D = disopyramide; D/C = discontinue; HOCM = hypertrophic obstructive cardiomyopathy; HTN = hypertension; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MI = myocardial infarction; MVP = mitral valve prolapse; NL = normal; P = procainamide; PACE = permanent pacemaker; PB = phenobarbital; PH = phenytoin; PR = propranolol; Q = quinidine; RB + LAHB = right bundle with left anterior hemiblock; RB + LPHB = right bundle with left posterior hemiblock; RHD = rheumatic heart disease; SA ENT = sinoatrial entrance; SACT = sinoatrial conduction time; SARC = sarcoidosis; T = tocainide; VF = ventricular fibrillation; VT = ventricular tachycardia.

* Unsustained ventricular tachycardia lasting 8 to 21 beats. † Postpacing pauses in the third through ninth complexes after overdrive pacing at a cycle length of 400 ms. ‡ Frequent protein meals to prevent hypoglycemia.

Electrophysiologic testing: After obtaining informed consent, patients were studied in the fasting state without premedication. Except for 1 instance, antiarrhythmic drugs and digoxin had been discontinued for 5 drug half-lives before electrophysiologic study (1 patient was studied while taking quinidine). Two 6 French quadripolar electrode catheters were inserted with use of the Seldinger technique into the femoral vein and positioned against the high right atrium and across the tricupsid valve to record the His bundle potential. A 5 French, 10 cm arterial line was placed percutaneously into the femoral artery to monitor arterial pressure. Scalar ECG leads V_1, I, and III, intracardiac recordings from the high right atrium and His bundle region, along with arterial pressure were simultaneously displayed on an Electronics for Medicine DR 12 ocsilloscope and recorded simultaneously at a paper speed of 100 to 200 mm/s. Pacing was accomplished by means of a programmable stimulator (Bloom, Narberth, Pennsylvania) with a pulse duration of 2 ms at 2 to 3 times diastolic threshold.

Baseline atrioventricular nodal and infranodal (HQ) conduction times were recorded and sinus node function was assessed.[2] The sinus nodal recovery time was determined at paced cycle lengths from 700 to 350 ms, at 50 ms decrements. The subsequent 9 postpacing intervals were analyzed for the presence of secondary pauses.[18] Sinoatrial conduction time was determined by both the extrastimulus and overdrive technique.[19,20]

Atrioventricular nodal and infranodal conduction were assessed during right atrial overdrive pacing at cycle lengths from 700 to 300 ms. Atrioventricular nodal refractoriness was determined during atrial overdrive pacing at a paced cycle length of 500 ms by scanning diastole with single atrial extrastimuli at 10 ms decrements.

Attempts to induce supraventricular tachycardia were carried out by sequentially scanning diastole with 1 or 2 atrial extrastimuli during normal sinus rhythm and during atrial pacing at a cycle length of 500 ms.

The high right atrial catheter was then positioned in the right ventricular apex. Attempts to provoke VT were accomplished by scanning diastole with 1, 2, or 3 ventricular extrastimuli during ventricular overdrive pacing at a cycle length of 500 ms. If the introduction of extrastimuli failed to induce VT, patients underwent burst ventricular pacing (10 to 15 beats) at cycle lengths varying from 500 to 250 ms. As of June 1980, the ventricular stimulation protocol was altered to include left ventricular stimulation in patients who had no inducible or unsustained VT during right ventricular stimulation. Also, if patients had no inducible VT during both right and left ventricular stimulation, the protocol was repeated during an isoproterenol infusion that increased the intrinsic heart rate to 115 to 125 beats/min.

Of the 15 patients considered for left ventricular stimulation, 2 patients did not consent, and 3 patients had atherosclerotic femoral arterial changes which prevented passage of the electrode catheter. In 8 patients with no inducible VT during right ventricular stimulation and in 2 patients with unsustained VT during right ventricular stimulation, left ventricular stimulation was performed. This was accomplished by inserting a 6 French bipolar Goetz catheter into a femoral artery through a sheath and positioning the catheter against the left ventricular apex. The left ventricular stimulation protocol was the same as that outlined for the right ventricle. All patients were given intravenous heparin (3,500 units) during the left ventricular stimulation studies.

Eight patients had no inducible VT with both right and left ventricular stimulation and were considered candidates for repeat stimulation with isoproterenol. Because of coronary artery disease (2 patients), hypertension (1 patient), and failure to consent (1 patient), only 4 patients underwent ventricular stimulation during an isoproterenol infusion. Sustained VT was defined as tachycardia lasting more than 30 seconds or requiring termination by overdrive pacing or electrical cardioversion because of hemodynamic compromise. Unsustained VT was defined as 6 or more consecutive provoked ventricular depolarizations.

At the conclusion of the study, patients with inducible VT underwent serial laboratory electrophysiologic studies to determine an effective antiarrhythmic regimen.[14,15] In patients with abnormalities of sinoatrial conduction or secondary pauses, the decision to permanently pace the patient was left to the judgment of the referring physician. If the infranodal conduction time was markedly prolonged (HQ >70 ms), permanent pacing was recommended, but the final decision was made by the patient's physician. The results of the study in the remainder of the patients were discussed with the referring physician, and subsequent therapy was based on either the study results or the physician's desires. Patients were followed at 3-month intervals, either by 1 of the authors or the referring physician, for a minimum of 16 months.

For the purpose of this study, any patient with the lone abnormal electrophysiologic finding of a prolonged HQ interval (HQ >55 ms) was considered to have a nondiagnostic study. Statistical analysis for association of clinical variables and electrophysiologic findings was performed using McNemar's test for correlated proportions.

Results

Inducible VT: The electrophysiologic diagnosis, treatment, and follow-up information for the 32 patients is outlined in Table I. The most significant finding of the study was the inducibility of VT in 11 patients. Ten patients had VT provoked with right ventricular extrastimuli (8 patients required 3 extrastimuli and 2 required 2 extrastimuli) and 1 patient had VT induced during right ventricular overdrive pacing at a cycle length of 310 ms. Stimulation of the left ventricle and stimulation during an isoproterenol infusion did not result in VT in any patient. VT was sustained in 7 pa-

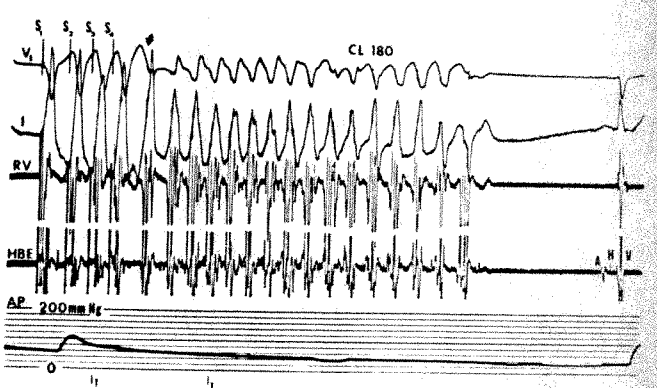

FIGURE 1. Induction of unsustained VT in patient 11 in the baseline state. **Tracings from top to bottom** represent recordings from surface ECG leads V_1 and I, the right ventricular apex (RV), and the His bundle electrogram (HBE). Arterial pressure is displayed on a horizontal grid scale of 0 to 200 mm Hg. The introduction of 3 ventricular extrastimuli produces a 16-beat episode (beginning at the **black arrow**) of VT at a cycle length (CL) of 180 ms. The episode persists for 3 seconds and is accompanied by a fall in arterial pressure from 110 systolic to 30 mm Hg. The episode of VT spontaneously converts to sinus rhythm.

tients and unsustained in 4 patients (Fig. 1). The episodes of sustained VT had an average cycle length of 224 ± 23 ms and required electrical cardioversion in 5 of 7 patients. Patients with unsustained VT had a tachycardia cycle length of 240 ± 38 ms and the episodes averaged 16.3 ± 3.0 beats. In all patients with unsustained VT there was a rapid fall in arterial pressure coincident with the arrhythmia (Fig. 1).

The average age of patients with inducible VT was 63.8 ± 5.4 years. All but 2 of the patients had evidence of organic heart disease by the initial screening tests. Because of the study design, none of the patients with inducible VT had previous evidence of VT during the continuous ECG monitoring. All of these patients had <10 premature ventricular depolarizations per hour during the monitoring period, and only 2 patients had ventricular couplets.

Five of the 11 patients with VT had been taking antiarrhythmic agents during at least 1 of the recorded syncopal spells; 3 patients were receiving no medications, and 3 were taking digoxin and furosemide. The left ventricular ejection fraction was normal (>50%) in 8 patients, and ranged from 35 to 45% in the remaining 3 patients.

The 11 patients with inducible VT underwent a total of 19 stimulation studies to design an effective antiarrhythmic regimen. Eight of 11 patients were placed on a regimen that completely suppressed inducible VT. Two patients had inducible VT despite treatment with conventional medications and were placed on chronic oral amiodarone therapy. One patient was incompletely protected from inducible VT with procainamide therapy, but refused to undergo further pharmacologic testing. In this patient the initial VT cycle length was 350 ms and the duration was 20 beats. After procainamide therapy the tachycardia cycle length increased to 450 ms and the duration was only 6 beats. Treatment with procainamide in this patient produced a junctional rhythm at 35 beats/min, and the patient received a prophylactic permanent pacemaker. Three additional patients with inducible VT also had permanent pacemakers implanted. One patient had an increase of the HQ interval from 85 to 110 ms after treatment with procainamide and amiodarone. Two other patients with bundle branch block and inducible VT (HQ intervals of 80 and 70 ms) received permanent pacemakers at the request of the referring physician.

The treatment and follow-up information for patients with abnormal electrophysiologic studies is illustrated in Figure 2. Patients were followed after the electrophysiologic study for 21.3 ± 1.2 months (range 16 to 36). Ten of the 11 patients with inducible VT are asymptomatic and have not had recurrent syncope during the follow-up period. One patient with inducible VT and a permanent pacemaker for right bundle branch block with left anterior hemiblock died. This patient discontinued the prescribed procainamide therapy 6 months after its initiation, and 1 month later presented with ventricular fibrillation.

One patient received quinidine therapy for atrial fibrillation during the reported syncopal episode. The patient underwent complete invasive testing while taking quinidine and again after the quinidine was discontinued. With the quinidine the patient had reproducible unsustained VT during right ventricular stimulation. The provoked VT had a cycle length of 240 ms and was 11 seconds in duration. A repeat study after quinidine was discontinued revealed no inducible VT during either right or left ventricular stimulation. At the request of the referring physician, the patient received a permanent pacemaker because of left bundle branch block (HQ interval 70 ms). This patient died during the fifth month of follow-up from an acute myocardial infarction.

Patients with clinical evidence of heart disease and those with a prolonged HQ interval had a significantly higher incidence of inducible VT ($p < 0.05$; Table II). In addition, inducible VT was more common in older patients (>50 years old) and in patients with abnormal electrocardiograms. Because of the small number of patients in each subgroup, these latter 2 associations did not reach statistical significance (Table II).

An analysis of the Holter monitor recordings of patients with and without inducible VT failed to reveal any significant difference in the frequency, prematurity, or repetitive nature of the premature ventricular depolarizations. The exclusion from the protocol of patients with frequent premature ventricular depolarizations was probably responsible for the latter observation.

Sinus node dysfunction and atrioventricular block: Five patients had evidence of sinus nodal dysfunction during invasive testing, which was not apparent during the monitoring period. None of these patients had an abnormality in sinus node recovery time, but 1 had abnormal secondary pauses. Two patients had sinoatrial entrance block, and 2 had abnormal sinoatrial conduction times demonstrated by the extrastimulus technique. Three of these patients had no underlying heart disease, 1 had coronary artery disease, and 1 had mild hypertension (taking no medications).

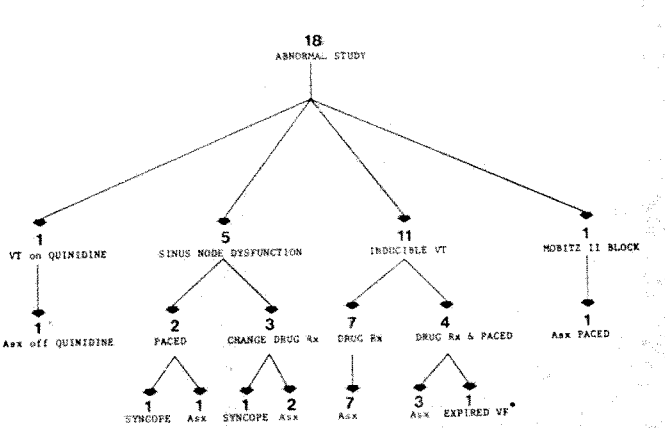

FIGURE 2. Schematic representation of the diagnosis, treatment, and follow-up in 18 patients with an abnormal electrophysiologic finding. Abbreviations are the same as in Table I, with the addition that Asx denotes asymptomatic. The **asterisk** indicates a patient who died after having discontinued the prescribed procainamide therapy.

Therapy varied in this subgroup of patients. Two patients received permanent pacemakers, 1 patient's previous propranolol therapy was discontinued and 2 patients were observed with no treatment. During the follow-up period (Fig. 2), 1 patient with a normally functioning pacemaker had recurrent syncope (at 9 months of follow-up) and 1 patient who was observed without specific treatment had recurrent syncope (at 2 months of follow-up). The remaining 3 patients were asymptomatic.

One patient with coronary artery disease and right bundle branch block with left anterior hemiblock (HQ interval of 60 ms) had infra-His block induced during right atrial overdrive pacing. During atrial overdrive pacing at a cycle length of 480 ms, periods of 1 to 1 atrioventricular conduction were spontaneously interrupted by periods of 2 to 1 infra-His block. The patient was asymptomatic 36 months after pacemaker implanation.

Patients with normal and nondiagnostic electrophysiologic studies: The remaining 14 patients had either normal (12 patients) or nondiagnostic (2 patients) electrophysiologic studies, and were treated empirically. The treatment and follow-up of these patients are summarized in Figure 3. Four of these patients received permanent pacemakers. A patient with systemic sarcoidosis and left bundle branch block (HQ interval 75 ms) was asymptomatic 20 months after pacemaker implantation. Three patients with recurrent syncope, but normal electrophysiologic studies (HQ interval 35 to 40 ms) underwent pacemaker insertion at the request of the referring physician. Two of these patients had recurrent syncope during the follow-up (6 and 12 months) and the other is asymptomatic. Three patients were taking quinidine for atrial premature depolarizations at the time of the recorded syncopal episodes, but none had a prolonged QT interval. Electrophysiologic testing was normal in these patients in the absence of quinidine and they have remained asymptomatic since chronic quinidine therapy was discontinued. One patient was found to have hypoglycemia (serum glucose level 35 mg/100 ml) during a subsequent presyncopal episode and is now asymptomatic on a high protein diet. Of the remaining 6 patients with normal electrophysiologic studies, 1 patient was asymptomatic with no treatment, 2 patients were asymptomatic with empiric procainamide therapy, and 1 patient was asymptomatic with aspirin therapy. The remaining 2 patients have had multiple recurrent syncopal episodes despite empiric therapy with antiarrhythmics, aspirin, and anticonvulsants.

Discussion

The cause of syncope is often apparent after obtaining a complete medical history and physical examination.[21–23] In patients without an obvious cause of syncope, ambulatory ECG monitoring has provided a probable cause in 48 to 64% of patients.[24,25] Despite this improvement in diagnostic ability, a significant percentage of patients with syncope have no discernible cause.

The present study was designed to evaluate the select subgroup of patients with recurrent syncope in whom there was no obvious cause. Since the patient selection critically affects the study's results and conclusions, we attempted to set stringent inclusion criteria yet still have a representative sample of patients with syncope. Consequently, patients with previously documented causes were excluded from the study. The long period of continuous ECG monitoring was designed to eliminate patients with easily detectable sinus nodal dysfunction, atrioventricular block, and frequent tachyarrhythmias. Patients with underlying bundle branch block, on the other hand, were accepted into the study if there was no evidence of second- or third-degree atrioventricular block during the course of the evaluation. By ensuring that the cause of syncope was "unknown" in our study group, the sensitivity of the electrophysiologic study could be evaluated. In addition, by selecting patients with recurrent syncope (26 of 32 patients), treatment interventions could be accurately evaluated over an appropriate clinical follow-up period.

TABLE II Association of Clinical and Laboratory Variables With Inducible VT

Clinical or Laboratory Variable	Incidence of VT	
Heart disease present	53% (9/17)	
Heart disease absent	13% (2/15)	$p < 0.05$
HQ >55 ms	64% (7/11)	
HQ ≤55 ms	19% (4/21)	$p < 0.05$
Age >50 yr	41% (9/22)	
Age ≤50 yr	20% (2/10)	NS
Abnormal ECG	47% (8/17)	
Normal ECG	20% (3/15)	NS

The ratio within the parentheses represents the number of patients with VT (numerator) and the number of patients with the descriptive parameter (denominator). NS = not significant.

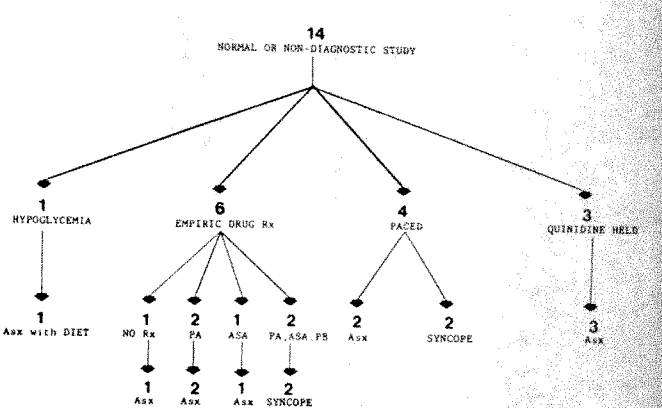

FIGURE 3. Schematic representation of the treatment and follow-up in 14 patients with a normal or nondiagnostic electrophysiologic study. Abbreviations are as in Table I and Figure 2. See text for details.

VT as a cause of syncope: The most significant finding in our study was the demonstration of laboratory-induced VT in 11 of 32 patients. Since 9 of the 11 patients had evidence of organic heart disease, this finding may have been a laboratory phenomenon related to the ventricular stimulation technique and not to the patient's clinical syncope. This explanation seems unlikely for 2 reasons. First, Vandepol et al[26] and Fisher et al[13] recently reported on the specificity of ventricular stimulation studies in control groups of patients with organic heart disease. Of 509 such patients studied, only 5 had inducible VT in the laboratory (2 of these 5 patients had a history of unexplained syncope). Because neither investigator routinely employed 3 extrastimuli in their studies, the reported specificity of 99% may not apply to our stimulation protocol. However, it is unlikely that our protocol produced a false-positive study in 34% of the patients.

The follow-up information provides further support that the laboratory induction of VT was related to our patients' syncope. After laboratory-directed antiarrhythmic therapy was initiated, no patient had a subsequent syncopal episode with the tested regimen. These follow-up data are complicated by the fact that 4 of these patients also received permanent pacemakers. Thus, relief of symptoms in these 4 patients cannot be solely credited to the prevention of occult VT. However, 1 of these 4 patients did have recurrent syncope and ventricular fibrillation after discontinuing the prescribed procainamide. The remaining 7 patients with inducible VT were treated with only the laboratory-directed antiarrhythmic regimen; all 7 have remained asymptomatic. Since syncope had been recurrent in 6 of these 7 patients, the absence of symptoms in the follow-up period is indirect evidence that VT was the cause of syncope. An additional observation is that 5 of these 7 patients had previously been treated with empiric antiarrhythmic therapy, but despite therapy had recurrent syncope. Only when these 5 patients were treated with a drug regimen that suppressed the laboratory induction of VT did their syncope abate. Thus, laboratory induction of VT not only provided a diagnosis in these patients, but also a rational basis for effective therapy.

The observation of unsustained VT in the laboratory is consistent with the clinical setting of brief episodes of loss of consciousness. However, in the 7 patients with sustained VT, either rapid overdrive pacing (2 patients) or electrical cardioversion (5 patients) was required to terminate the patient's laboratory arrhythmia. What would have occurred in these patients with further observation is only conjecture, but perhaps neural, metabolic, or cardiac factors would have resulted in spontaneous conversion to sinus rhythm. In subsequent patients (not included in this study), we have occasionally observed spontaneous conversion of laboratory-induced VT to sinus rhythm after 30 to 40 seconds without external intervention. We hypothesize that spontaneous conversion probably occurred in the study patients during their clinical episodes of syncope. An alternative explanation is that the clinical VT is unsustained (possibly an effect of antiarrhythmic drugs in some patients), but the laboratory VT is sustained in the baseline state.

In our study group, VT was more commonly found in older patients, in patients with an abnormal baseline electrocardiogram, and in patients with an abnormal HQ interval. These factors are probably not independent predictors of VT, but rather reflect the presence of the underlying organic heart disease. In addition, our laboratory protocol included the introduction of up to 3 ventricular extrastimuli at multiple coupling intervals in order to facilitate the induction of VT. A less aggressive ventricular pacing protocol, particularly in a group of young patients with syncope and without organic heart disease, would probably yield a lower incidence of VT.

Sinus node dysfunction and bundle branch block: Because the study design excluded patients with extreme bradycardia and obvious sinus node dysfunction, the abnormalities discovered with sinus node testing were subtle. Although several studies suggest that implantation of permanent pacemakers will relieve symptoms of dizziness and syncope in patients with abnormal sinus node function, others have demonstrated no improvement in symptoms.[27] Since detected abnormalities in sinus node function and symptoms are not always related, pacemaker implantation was not performed in all our patients. From the follow-up information in our small group of patients, it is not clear whether the observed electrophysiologic abnormalities were related to the clinical symptoms.

Of the 7 patients presenting with syncope and bundle branch block, only 1 had infra-His block during right atrial overdrive pacing. Dhingra et al[28] reported this finding in 15 of 496 patients with bundle branch block undergoing electrophysiologic study. During a 3.4 year follow-up, 7 of these 15 patients progressed to symptomatic complete atrioventricular block. Thus, intermittent complete atrioventricular block was the probable cause of syncope in our patient. Our remaining 6 patients with bundle branch block also underwent permanent pacemaker implantation. Since 5 of these 6 patients had other demonstrable causes of syncope, the efficacy of pacemaker insertion cannot be adequately evaluated. Identification of a possible cause of syncope other than progression to complete atrioventricular block is consistent with reports in the literature. In studies by Scheinman et al[16] and Dhingra et al[29] only a small percentage of patients with bundle branch block and syncope had documented progression to high-degree atrioventricular block. The cause was either unknown or secondary to other disorders in the remainder of their patients. While there appears to be a general consensus that patients with bundle branch block and recurrent syncope should be treated with a permanent ventricular pacemaker, our observation would support the need for detailed electrophysiologic studies in these patients. As a result of such studies, the physician should decide whether optimal therapy includes a permanent pacemaker with or without antiarrhythmic drugs.

Other investigators have employed similar techniques in evaluating patients with syncope.[30,31] In a study of

25 patients with recurrent syncope, DiMarco et al[30] reported a presumptive diagnosis in 17 patients. Because these investigators included a prolonged atrioventricular nodal refactory period and a prolonged HQ interval as causes of syncope, the reported sensitivity of their protocol (68%) exceeds that of the present study (56%). Since it remains controversial whether these laboratory abnormalities are related to clinical symptoms, similar abnormalities were not considered of diagnostic value in our study. A second difference between the 2 studies relates to the patient follow-up. In these types of studies, evidence supportive of a presumptive diagnosis is obtained by monitoring patients for the recurrence of symptoms during treatment. In DiMarco's study, patients with inducible VT were followed for abbreviated periods, with 5 of 9 such patients being followed for only 6 months or less. In contrast, patients with inducible VT in the present study were followed for a minimum of 16 months, with an average follow-up of 20.1 ± 1.8 months. The absence of syncope during our treatment period provides stronger indirect evidence that this laboratory-induced arrhythmia was the cause of the clinical symptoms.

In our series, complete electrophysiologic studies resulted in definitive findings in 18 of 32 patients. Two of these patients died during the follow-up, and 14 of the remaining 16 are asymptomatic on laboratory-directed therapy. The most commonly detected abnormality was occult VT, and the response of patients with this finding to laboratory-directed antiarrhythmic therapy was excellent. Our observations demonstrate the value of invasive electrophysiologic studies in determining the cause and guiding therapy in patients with syncope of undetermined origin. These studies may allow for rapid diagnosis and institution of appropriate therapy and thus avoid the costs of repeated hospitalization or Holter examinations as well as the morbidity resulting from recurrent syncope. We believe provocative electrophysiologic studies are useful in selected patients with recurrent syncope in whom the conventional evaluation has been unrevealing.

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Value of the H-Q Interval in Patients With Bundle Branch Block and the Role of Prophylactic Permanent Pacing

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His bundle electrograms were obtained in 313 patients with chronic bundle branch block who were followed for a mean period of almost 3 years. The infranodal conduction time (H-Q interval) was <55 ms in 97 patients (Group I), 55 to 69 ms in 99 patients (Group II), and ≥70 ms in 117 patients (Group III). There was a higher incidence of organic heart disease in patients in Group III, but the groups were otherwise comparable. On follow-up study, mortality and the incidence of sudden death were similar among the groups, but patients in Group III had a greater incidence of progression to high degree atrioventricular block (HDB) than did those in Groups I and II (14 of 117 [12%] versus 4 of 97 [4%] and 2 of 99 [2%], p <0.01, respectively). High degree block was found in 4 of 17 (24%) patients with an H-Q interval (H-Q) ≥100 ms.

Sixty-two patients underwent permanent prophylactic pacemaker insertion at the discretion of the referring physician and were compared with 231 patients who did not. Paced patients had a higher incidence of transient neurologic symptoms and prolonged H-Q, but the groups were otherwise comparable. On follow-up study, mortality and the incidence of sudden death were similar among the groups, but symptom relief was significantly more common among patients with pacemakers.

In conclusion, in our population (1) H-Q ≥70 ms was an independent risk factor for progression to HDB, (2) H-Q ≥100 ms identified a subgroup at particularly high risk, and (3) prophylactic pacemakers relieved neurologic symptoms but did not prolong life.

Patients with chronic bundle branch block have an increased risk for the development of complete atrioventricular (AV) block.[1–5] The recent introduction of techniques for ready recording of the His bundle potential in man has been applied to patients with bundle branch block.[6,7] Prolongation of the infranodal conduction time in a patient with bundle branch block signifies associated disease in either the unblocked bundle branch or the His bundle. Theoretically, a prolonged H-Q interval suggests advanced conduction system disease and may conceivably identify a subgroup at high risk for developing AV block or sudden death. The clinical significance of H-Q prolongation remains controversial.[8–10] We previously reported short-term prospective follow-up data in patients with chronic bundle branch block who underwent His bundle recordings.[11] In the present report, this experience is updated with a larger cohort to appraise the clinical significance of a prolonged H-Q interval more accurately. In addition, we are updating our experience with prophylactic permanent pacing in these patients.[12]

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Methods

The methodology for this study was described in detail previously.[11] In brief, all patients with the electrocardiographic pattern of chronic bundle branch block were included in the present study. Patients from the cardiology clinics of various San Francisco Bay Area hospitals as well as patients referred for electrophysiologic study were included. Patients with bundle branch block and acute myocardial infarction as well as those with second or third degree AV block were excluded from the study.

A complete history, chest roentgenogram, and physical examination were obtained in all patients. His bundle electrograms were obtained using standard techniques. In brief, a multipolar electrode catheter was inserted into the right femoral vein and positioned across the tricuspid valve. The His bundle electrogram and 3 surface electrocardiographic leads were displayed simultaneously on an oscilloscope and recorded (Electronics for Medicine VR-12 recorder). The AV nodal conduction time was measured from the initial high frequency deflection of the low right atrial electrogram to the first high frequency His bundle deflection (A-H), whereas infranodal conduction time was measured from the initial high frequency deflection recorded from the His bundle to the earliest onset of ventricular activation determined from the surface leads (H-Q). Patients who had second and third degree AV block during the His bundle recording were also excluded from study.

Follow-up study: Patients were followed up every 3 months either in the pacemaker and arrhythmia clinic or by referring physicians. Follow-up information was obtained by a public health nurse from patients who did not keep scheduled appointments. When necessary, home visits were made to obtain additional information including 12-lead electrocardiograms. In the event of progression to a higher degree of AV block, electrocardiographic tracings showing AV block were obtained. The diagnosis of second or third degree infranodal block was made on the basis of typical Mobitz type II AV block or periods of complete AV block with slow idioventricular rhythm associated with a different QRS morphology. Only patients with spontaneous AV block were included for study. Excluded were patients who showed AV block in the course of acute myocardial infarction or those with associated electrolyte disorders. In 6 patients the infranodal site of block was confirmed at the time of repeat electrophysiologic study. Patients requiring pacemaker insertion for sinus node disease or those in whom block developed at the level of the AV node were excluded from the study. In the event of death, hospital or coroner's reports, or both, were reviewed and observers were interviewed to determine if death was sudden.

Definitions: The criteria for diagnosis of bundle branch or fascicular block as well as intraventricular conduction delay have been discussed elsewhere.[13]

Congestive heart failure was diagnosed on the basis of physical findings and chest roentgenograms, and the patients were categorized according to the New York Heart Association functional classification. The diagnosis of valvular heart disease was based on physical examination or the results of cardiac catheterization. The diagnosis of cardiomyopathy was made in those patients with myocardial disease without demonstrable cause. For purposes of this study, patients with a history of smoking in excess of 10 cigarettes a day were classified as cigarette smokers. *Sudden death* was defined as unexpected natural death occurring either instantaneously (during sleep) or within 1 hour of the onset of symptoms. *Cardiovascular deaths* were those due to acute myocardial infarction or congestive heart failure.

Sixty-two patients underwent prophylactic pacemaker insertion. None of these patients showed evidence of second or third degree AV block during repeated continuous electrocardiographic monitoring. Pacemaker insertion was performed at the discretion of the referring physician on the basis of neurologic symptoms (syncope, recurrent dizzy spells, or seizures) or electrophysiologic abnormalities, or both. In some patients without symptoms, the nature of their occupation proved to be an important factor in the decision to insert a permanent pacemaker. These patients were seen regularly either by their private physicians or in an arrhythmia and pacemaker clinic. In addition, follow-up study included periodic telephone transmission of the pacemaker rate and stimulus characteristics.

Statistical methods: All data were stored on punch cards and later retrieved using a program written for the IBM model 360/75 computer. All nominal data were tested with the chi-square test or, when numbers were small, with Fisher's exact probability test.[14]

Results

A total of 367 patients with bundle branch block have been entered into the study since March 1972. Twenty-three patients were lost to follow-up study and 19 were excluded either because pacemakers were inserted for sinus node disease (12 patients) or because AV nodal block was demonstrated at repeat study (7 patients). Similarly, 12 patients in whom second or third degree AV block developed as a result of electrolyte abnormality or acute myocardial infarction were not included in the present analysis. The remaining 313 patients form the basis of this report.

TABLE I Clinical and Electrophysiologic Data in Patients With Chronic Bundle Branch Block

Variable	Group I: H-Q 30–54 ms		Group II: H-Q 55–69 ms		Group III: H-Q >70 ms		p Value
	n	%	n	%	n	%	
Patients (n)	97	...	99	...	117	...	
Age (mean ± SD) (yr)	66 ± 13	...	66.6 ± 14	...	66.5 ± 11	...	NS
Total with organic cardiac disease*	85	88	87	88	104	89	NS
Coronary artery disease	63	65	68	67	78	69	NS
Transient neurologic symptoms	58	60	58	59	68	56	NS
Syncope	38	39	40	40	46	39	NS
Congestive heart failure (class III or IV)	18	18.5	22	22	38	32	<0.05†
Follow-up (mo)	34 ± 24	...	34.5 ± 27	...	28 ± 23	...	NS
Progression to 2° or 3° block	4	4	2	2	14	12	<0.001†
Sudden deaths	12/97	14	12/99	12	19/117	16	NS
Cardiac deaths	14/97	14	15/99	15	28/117	24	NS
All deaths	41	42	50	51	57	49	NS

* Organic cardiac disease included patients with coronary artery, primary myocardial, valvular, hypertensive, and congenital heart disease.
† The incidence of organic cardiac disease, severe congestive heart failure, and progression to second (2°) or third degree (3°) AV block was higher in Group III than in either Group I or II.
NS = not significant; SD = standard deviation.

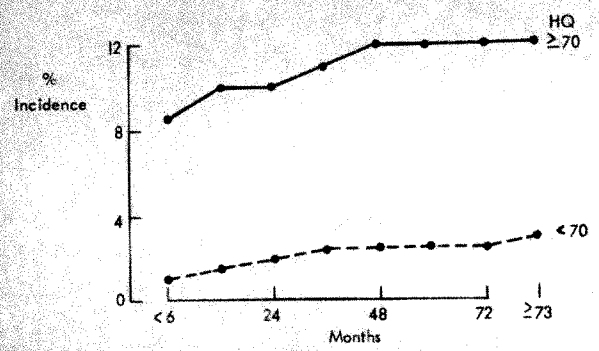

FIGURE 1. Incidence of spontaneous progression to second or third degree infranodal block with in patients an H-Q interval ≥70 ms is compared with that in patients with an H-Q interval <70 ms. The bulk of progression occurs within 6 months of entry into the study.

The patients were divided into 3 groups on the basis of the H-Q interval (Table I). Ninety-seven patients had H-Q intervals of 30 to 54 ms (Group I), 99 had H-Q intervals of 55 to 69 ms (Group II), and 117 had H-Q intervals ≥70 ms (Group III). There was no significant difference in age, incidence of syncope, or transient neurologic symptoms or length of follow-up study among the groups. The majority of subjects had organic heart disease; the most common diagnosis was coronary artery disease (67%).

The incidence of spontaneous progression to second degree or complete AV block was significantly higher in Group III (14 of 117 or 12%) than in Groups I (4 of 97 or 4%) and II (2 of 99 or 2%) ($p < 0.001$). The cumulative incidence of progression to second or third degree AV block for patients with H-Q ≥70 ms and those with H-Q <70 ms is detailed in Figure 1. The bulk of progression occurred in Group III patients within 6 months after entry into the study. Thereafter, a more gradual rate of progression was observed until plateau levels were achieved in both groups after approximately 36 months. The "plateau" may reflect the smaller numbers of subjects still alive at this time.

The risk of progression appears to be quantitatively related to the degree of H-Q lengthening once a critical H-Q interval of 70 ms is exceeded. For example, 17 patients with an H-Q interval of ≥100 ms showed a 23.5% progression rate (4 of 17) over a mean follow-up period of 22 ± 17 months. Most of the patients (13 of 17) had transient neurologic symptoms. Four of 17 had spontaneous progression to second or third degree AV block 11, 12, 18, and 56 months after entry and received pacemakers. Two of the 4 died of severe congestive heart failure. Seven of the 17 patients had prophylactic pacing; of the 7, 6 had transient neurologic symptoms. Five patients died. Three deaths were due to cardiac causes and 2 to noncardiac causes; none died suddenly. Three of 6 patients who did not have pacing died suddenly. Although the group of patients with an H-Q interval of ≥100 ms form a small subgroup within the total study group (17 of 313 [5.1%]), the high spontaneous progression rate is a minimal figure because over half of these patients were treated with prophylactic pacing.

The incidence of sudden death was similar among the groups (Table I). Although total cardiac mortality was higher in patients with marked prolongation of the H-Q interval (Group III) than in the other groups, this difference was not statistically significant. The possibly higher cardiac mortality in Group III may be related to the higher incidence of severe congestive heart failure in this group than in the others (Table I).

The surface electrocardiographic pattern proved to be of limited value in predicting either spontaneous progression to second or third degree AV block or the presence of marked prolongation of the H-Q interval. The various electrocardiographic patterns for each group are summarized in Table II. First degree AV block was significantly more frequent in Group III than in Group I, but this finding proved of limited clinical value. Similarly, there was no significant difference in the incidence of left bundle branch block or a bifascicular block pattern among the 3 groups.

These data identify a subset of patients with bundle branch block at increased risk for the development of AV block and in whom permanent pacemaker insertion might conceivably improve neurologic symptoms and survival. To test this hypothesis, we examined the clinical course of patients in whom permanent pacemakers were inserted prophylactically (in the absence of documented high grade AV block) and unpaced patients. Prophylactic pacemakers were inserted at the discretion of the referring physicians on the basis of

TABLE II Electrocardiographic Patterns in Patients With Chronic Bundle Branch Block

Variable	Group I		Group II		Group III		p Value
	n	%	n	%	n	%	
Patients (n)	97	...	99	...	117	...	...
First degree AV block	26	27	45	45	65	56	<0.001*
Right bundle branch block	22	23	34	34	49	42	<0.02*
Left bundle branch block	29	30	17	17	21	18	NS
Right bundle branch block with left anterior hemiblock	33	34	36	35	29	25	NS
Right bundle branch block with left posterior hemiblock	7	7	5	4	7	6	NS
Intraventricular conduction defect	6	6	7	7	11	9	NS

* There was no significant difference between Groups II and III. However, Group III had a higher incidence of first degree AV block and right bundle branch block than Group I.

TABLE III Comparison of Clinical and Electrophysiologic Findings for Paced and Unpaced Patients

Clinical Variable	Paced Patients: Prophylactically n	%	Paced Patients: For Progression to Second or Third Degree AV Block n	%	Unpaced Patients n	%	p Value
Patients (n)	62	...	20	...	231	...	...
Age (mean ± SD) (yr)	67 ± 10	...	65 ± 13	...	66 ± 14	...	NS
Congestive heart failure (class III or IV)	16	26	6	30	61	26	NS
Syncope	41	66	4	20	80	35	<0.02
Transient neurologic symptoms	47	76	8	40	134	55	<0.01
H-Q (mean ± SD) (ms)	72 ± 24	...	78 ± 25	...	59 ± 16	...	<0.001
Follow-up period (mo)	29 ± 22	...	39 ± 34	...	32 ± 24	...	NS
Relief of syncope	36/41	88	4/4	100	43/80	53	<0.001
Relief of any neurologic symptoms	32/47	70	7/8	87	68/133	50	<0.01
Sudden deaths	12/62	19	1/20	5	30/231	13	NS
Cardiac deaths	12/62	19	7/20	35	44/231	19	NS
Total deaths	31	50	11	55	108	47	NS

neurologic symptoms or abnormal electrophysiologic findings, or both. No evidence of AV block was found despite repeated 24-hour continuous dynamic electrocardiographic monitoring or observation in a coronary care unit. Clinical and electrophysiologic data for paced and unpaced patients are shown in Table III.

The 62 patients who underwent prophylactic pacemaker insertion were similar with respect to age and cardiac diagnosis compared with the 231 patients who were not paced. Twenty patients who required permanent pacemaker insertion because of progression to second or third degree AV block were analyzed separately. As expected, the incidence of syncope or transient neurologic symptoms as well as an abnormal H-Q interval were greater in the group with prophylactic pacing (Table III). Patients treated with pacemakers had a significantly higher incidence of relief of any neurologic symptoms or syncope than did the unpaced group.

Figure 2 shows follow-up findings in symptomatic prophylactically paced and unpaced patients. Of note was the finding of a high incidence of spontaneous disappearance of symptoms for the unpaced group. In addition, follow-up evaluation revealed the probable causes of symptoms in approximately half of those patients who had persistent transient neurologic symptoms. The causes included episodes of tachyarrhythmia (8 patients), cerebrovascular disease (4 patients), orthostatic hypertension (1 patient), drug use including alcoholism (5 patients), and hypoglycemia (1 patient). Seven of the 8 patients with transient neurologic symptoms who underwent pacemaker insertion because

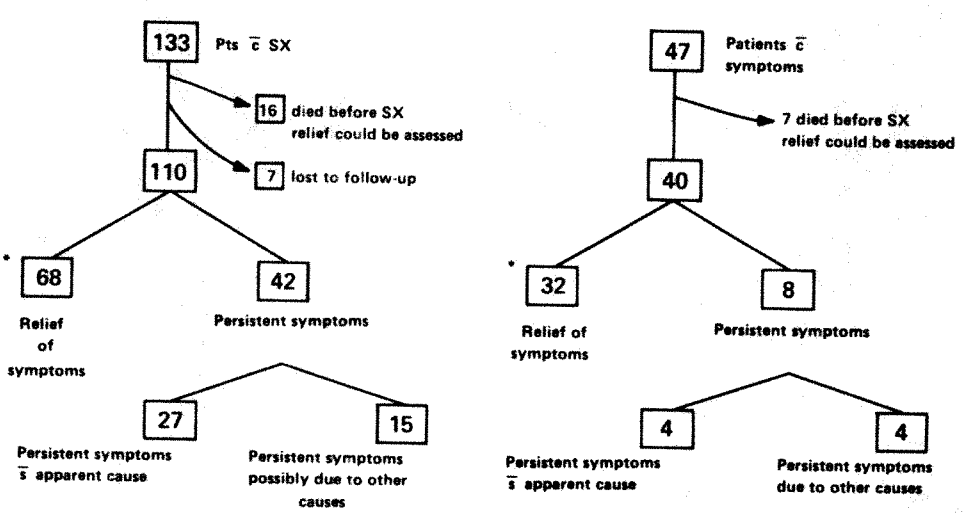

FIGURE 2. Follow-up chart of symptomatic patients who were either not paced (**left**) or paced (**right**). Excluded were 20 patients who underwent pacemaker insertion because of documented spontaneous trifascicular block. The incidence of relief of all transient neurologic symptoms was significantly higher in the paced group. SX = symptoms. **Asterisk** indicates $p < 0.05$.

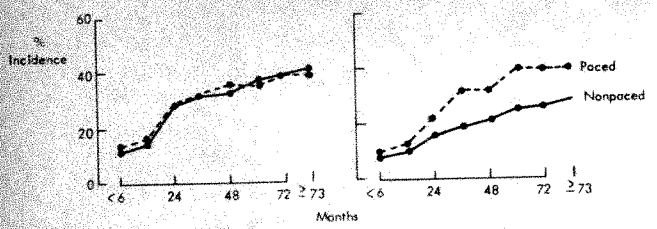

FIGURE 3. Cumulative incidences of cardiac deaths (**left**) and sudden deaths (**right**) for paced and unpaced patients. Although the incidence of sudden death was higher in paced patients at each follow-up interval, the differences were not significant.

of documented AV block had relief of symptoms (not shown in Figure 5).

Similar causes of transient neurologic symptoms were discerned in paced patients who had persistent symptoms after pacemaker insertion. We found no significant difference in the cumulative incidence of either cardiac or sudden deaths between paced and unpaced patients (Fig. 3). Sudden death was greater in the paced groups, but this difference was not significant.

It might reasonably be argued that the incidence of sudden death in the paced group might have been substantially higher had they not undergone prophylactic pacemaker insertion. We therefore compared all nonpaced patients with transient neurologic symptoms and an H-Q interval ≥70 ms with the paced group (Table IV). The 2 groups were comparable with regard to all clinical and electrophysiologic variables. The incidence of relief of syncope (88 versus 55%) and relief of all neurologic symptoms (89 versus 59%) was significantly greater in the paced group, but there was no difference in the incidence of sudden death or cardiac death between these 2 groups. Thus, we found no evidence tht prophylactic pacing increased longevity even when such patients were compared with a group with an expected increased risk for progressive conduction system disease.

Discussion

This report confirms and extends our previous observations relative to the importance of the H-Q interval in patients with bundle branch block. A markedly prolonged H-Q interval represents a clear-cut risk factor for spontaneous progression to second or third degree infranodal block. This increased risk was confined to those patients with an H-Q interval ≥70 ms, who had a 4-fold increase in progression compared with subjects who had either normal or slightly increased H-Q intervals (35 to 69 ms). A new and potentially important finding was the extremely high risk of progression to second or third degree AV block (23.5%) among patients with an H-Q interval ≥100 ms, suggesting a graded increment of risk dependent on the H-Q interval. It is pertinent to compare our data with those of 2 other similarly designed larger prospective studies of patients with bundle branch block.

Our findings confirm the recent report of Dhingra et al[15] involving 517 patients followed for a mean of 3.4 years. They also found an increased risk for spontaneous trifascicular block in patients with prolonged H-Q intervals. The incidence of spontaneous AV block in their study was lower than that in our series (that is, 0.6% for those with a normal H-Q interval versus 4.5% for those with H-V interval prolongation. In addition, our data differ with respect to the cumulative incidence of AV block. In our series, the bulk of spontaneous progression occurred within 6 months of study with a gradual increase to the 36th month of follow-up study followed by a plateau. In contrast, Dhingra et al[15] found a gradual increase in the cumulative incidence of AV block throughout the course of their study. Our results also differ from those of McAnulty et al,[16] who found that the H-Q interval failed to define a high risk subgroup (in terms of progression to complete AV block or sudden death) in 257 patients followed up over an average of 25 months. We believe that differences between studies are best reconciled by the characteristics of the respective

TABLE IV Prophylactically Paced Patients Versus Symptomatic Patients With an H-Q Interval ≥70 ms

Variable	Prophylactically Paced Patients		Unpaced Patients (H-Q ≥70 ms)		p Value
	n	%	n	%	
Patients (n)	62	...	37	...	...
Sex (male)	51	...	32	...	NS
Age (mean ± SD) (yr)	66 ± 11	...	64 ± 13	...	NS
Coronary artery disease	42	68	27	73	NS
Hypertension	23	37	15	41	NS
Diabetes	9	15	4	11	NS
Congestive heart failure (class III or IV)	16	26	13	35	NS
Syncope	41	66	20	54	NS
All transient neurologic symptoms	47	76	37	100	...
Relief of syncope	36/41	88	11/20	55	<0.05
Relief of all symptoms	32/40	59	20/34	59	<0.05
H-Q (mean ± SD) (ms)	72 ± 24	...	81 ± 12	...	<0.05
Follow-up period (mo)	29 ± 22	...	24 ± 23	...	NS
Sudden deaths	12/62	19	6/37	16	NS
Cardiac deaths	12/62	19	6/37	16	NS
Total deaths	31	50	14	38	NS

patient populations. Patients in the studies by McAnulty et al[16] and Dhingra et al[15] were recruited primarily by mass electrocardiographic screening. In contrast, most of our patients either were referred for study or consented to participate in the study because of symptoms. The ages of their patients as well as the incidence of organic cardiac disease, transient neurologic symptoms, and severe congestive heart failure were less than those in our studies. Earlier reports by Dhingra et al[17] and Denes et al,[18] for example, failed to show an increased risk for progression in those with a prolonged H-Q interval versus subjects with a normal H-Q interval. We hypothesize that as their patients aged, the respective population cohorts developed more similar characteristics which may help to explain the concordance in findings between our most recent studies. It is still a matter of conjecture whether or not the same will prove true for the patients followed up by McAnulty et al.[16] Similarly, the difference in the cumulative incidence of spontaneous AV block in our series compared with that of Dhingra et al[15] probably results from the higher incidence of syncope in our patients. In some of our patients, syncope was probably related to episodic high grade AV block that was eventually diagnosed relatively soon after entry into the study. Of special clinical importance was the finding of a very high incidence of spontaneous progression to complete AV block in patients with atrial pacing-induced AV block.[19]

In the present study, although prophylactic permanent pacing (in a subgroup with either symptoms or a prolonged H-Q interval or both) resulted in a significant decrease in the incidence of syncope, the incidence of sudden death or death was unchanged compared with that in the unpaced group. Similarly, the incidence of sudden death was comparable in the prophylactically paced group and in symptomatic patients with an H-Q interval ≥70 mm who were not treated with pacemakers. We interpret these findings as suggesting that the cause of sudden death was largely related to malignant ventricular arrhythmias, because no evidence of pacemaker malfunction was found in follow-up evaluation. In 2 paced patients undergoing continuous electrocardiographic monitoring, death was documented as due to ventricular fibrillation. These findings are in accord with the observations of Denes et al,[20] who concluded that death in patients with bifascicular block were largely due to ventricular arrhythmias; however, somewhat different results have been reported by other groups.[21,27]

Clinical implications: Conclusions from our data must be interpreted in the light of our study population: almost all had organic cardiac disease and most had transient neurologic symptoms. Therefore, our findings are not comparable to data of epidemiologic surveys of asymptomatic subjects with bundle branch block. In this study group, those with an H-Q interval ≥70 ms had a definite increased risk of progression to spontaneous trifascicular block compared with patients with an H-Q interval <70 ms. The overall risk of progression in patients with an H-Q interval ≥70 ms is still small, and routine prophylactic pacing in asymptomatic patients is not warranted. Transient neurologic symptoms alone may be an unreliable guide in determining the role of prophylactic pacing, because over half the patients with bundle branch block will have spontaneous remission of symptoms and a significant number have symptoms due to cardiac arrhythmias or neurologic, metabolic, or drug-related causes. These findings are in accord with the observations of Dhingra et al,[23] who found a high rate of spontaneous remission of symptoms. In patients with an H-Q interval ≥70 ms with recurrent transient neurologic symptoms (of no known cause), pacing appears to be indicated and will likely result in relief of symptoms, but there is no evidence to suggest that this intervention will prolong life. This conclusion is supported by our follow-up observations in 20 patients who received pacemakers because of documented progression to second or third degree AV block in that cardiac mortality was identical to that in unpaced or prophylactically paced patients; however, a trend toward a lower incidence of sudden death appeared in patients with documented AV block. The ultimate prognosis appears to be related to the severity of the underlying cardiac disease.[12] A new finding in our study is the extremely high incidence of spontaneous progression in those with an H-Q interval ≥100 ms. These patients, when symptomatic, should clearly undergo prophylactic pacemaker insertion.

Available data suggest 2 subgroups of patients with bundle branch block at very high risk for spontaneous trifascicular block. One group includes those with atrial pacing-induced infranodal block as described by Dhingra et al,[19] and the other is of patients with an H-Q interval ≥100 ms. Either of these findings is of great clinical value but unfortunately is only found in a miniscule percentage of patients with bundle branch block. Clearly, more effective means are required to identify patients with bundle branch block at high risk for second or third degree AV block or sudden death. For example, if sudden death is related to malignant ventricular arrhythmias, then perhaps Holter monitoring or ventricular stimulation studies[24] or both will prove of value in the detection of a subset of patients with bundle branch block and transient symptoms who are at increased risk for this complication.

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Effects of Verapamil on the Electrophysiologic Properties of the Accessory Pathway in Patients With the Wolff-Parkinson-White Syndrome

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The effects of intravenous verapamil on the electrophysiologic properties of the accessory pathway in 12 patients with symptomatic Wolff-Parkinson-White syndrome were studied using intracardiac electrical recordings. In 11 of the 12 patients it was possible to induce a reentrant supraventricular tachycardia with programmed atrial or ventricular pacing. After verapamil it was still possible to induce supraventricular tachycardia in 6 of the 11 patients; however, the mean cycle of length of the tachycardia increased from a control value of 330 ± 20 ms (mean ± standard error of mean) to 369 ± 21 ms ($p < 0.05$). Although verapamil had no significant effect on the anterograde refractory period of the accessory pathway as measured by the extrastimulus technique, it significantly increased maximal 1:1 atrioventricular (AV) conduction through the accessory pathway to incremental high rate atrial pacing in 10 of the 12 patients (control value 227 ± 10 beats/min, value after verapamil 258 ± 14 beats/min, $p < 0.001$). In 4 patients in whom episodes of atrial fibrillation could be compared before and after verapamil, the drug decreased the average R-R interval from a control value of 327 ± 27 ms to 282 ± 28 ms ($p < 0.05$) and decreased the shortest R-R interval between preexcited beats from a control value of 237 ± 21 ms to 209 ± 18 ms ($p < 0.05$).

It is concluded that in patients with symptomatic Wolff-Parkinson-White syndrome, verapamil may increase the ventricular response through the accessory pathway if atrial fibrillation occurs. This finding, which is of potential clinical significance, could not have been predicted from conventional anterograde refractory period estimations.

The calcium antagonist verapamil has proved an effective agent in the acute treatment of episodes of paroxysmal supraventricular tachycardia.[1–5] The drug is also sometimes used to prevent paroxysmal arrhythmias in patients with the Wolff-Parkinson-White syndrome. Despite its wide clinical use, uncertainty still exists regarding the safety of the drug in patients with this syndrome. Spurrell et al[6] reported that verapamil either lengthened or had no significant effect on the anterograde refractory period of the accessory pathway in 7 of 8 patients with the Wolff-Parkinson-White syndrome. In the remaining patient the refractory period decreased 35 ms. On this basis they concluded that verapamil was a safe drug to use in the majority of patients with Wolff-Parkinson-White syndrome. However, Henning et al[7] recently reported that verapamil increased the ventricular response to electrically induced atrial fibrillation in 7 patients with the Wolff-Parkinson-White syndrome and predominant conduction through the accessory pathway.

The purpose of this study was to assess the effects of verapamil on the electrophysiologic properties of the accessory pathway in patients with symptomatic Wolff-Parkinson-White syndrome. In particular, we evaluated the effect of the drug on maximal 1:1 atrioventricular (AV) conduction through the accessory pathway to incremental high rate atrial pacing and compared these results with those obtained by the conventional extrastimulus technique of measuring refractoriness.

Methods

Patient population: Twelve patients with symptomatic Wolff-Parkinson-White syndrome undergoing an electrophysiologic study form the basis of this report. The appro-

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TABLE I Patient Characteristics and Electrophysiologic Variables

Case	Age (yr) & Sex	Site of AP	Reason for Study	Anterograde ERP of AP (ms)		Max 1:1 AV Conduction via AP (beats/min)		Retrograde ERP of AP (ms)		Max 1:1 VA Conduction via AP (beats/min)		SVT Cycle Length (ms)	
				C	V	C	V	C	V	C	V	C	V
1	21M	Sept	PSVT	220	210	280	330	<230	<235	>230	>230	295	320
2	41M	Left	AF	<220	<245	230	270	245	240	>220	>220	390	...
3	24F	Right	PSVT	280	275	210	260	<265	<260	205	>220	310	370
4	30F	Left	PSVT	290	290	220	220	260	255	>220	>220	270	...
5	29M	Left	AF	295	300	230	280	275	275	>230	>230	350	...
6	27M	Left	PSVT	<240	<245	235	290	250	240	>220	>220	300	380
7	33M	Right	AT	290	290	235	280	<250	<245	>250	>250	350	...
8	26M	Left	AF	<220	<225	290	320	<250	<250	>250	>250	320	335
9	57M	Sept	AF	280	285	195	210	...	...	...	...	...	...
10	56M	Left	PSVT	290	290	245	260	<270	<260	>220	>220	320	...
11	24M	Left	PSVT	290	300	180	170	<240	<240	>250	>250	330	345
12	36F	Left	PSVT	310	305	185	205	<240	<240	>235	>250	430	465
Mean				283	283	227	258	258	253	...	...	330	369
Standard error				8.4	9.6	9.6	13.8	6.6	8.3	...	...	21.1	19.2
P value				NS		p <0.01		NS				p <0.05	

AF = atrial fibrillation; AP= accessory pathway; AT = antidromic tachycardia (see text); C = control; ERP = effective refractory period; Left = left free wall; Max = maximal; PSVT = paroxysmal supraventricular tachycardia; Right = right free wall; Sept = septal; SVT = supraventricular tachycardia; V = verapamil.

priate clinical details, indications for the electrophysiologic study, and sites of the accessory pathway are shown in Table I.

All patients had evidence of preexcitation on at least 1 baseline 12-lead electrocardiogram. In 2 patients the accessory pathway was located in the septal region, 3 patients had right free wall pathways, and 7 patients had left free wall pathways. In 7 patients the indication for study was recurrent episodes of supraventricular tachycardia with narrow width QRS complexes during the tachycardia. In 4 patients the indication for study was paroxysmal atrial fibrillation. The remaining patient (Patient 7) had episodes of regular width QRS complex tachycardia (rate 200 beats/min) with the QRS complexes during the tachycardia identical morphologically to the delta wave.

Electrophysiologic studies: Patients were studied in the postabsorptive, nonsedated state after informed written consent was obtained. All antiarrhythmic therapy was discontinued for at least 72 hours before the study. Three quadripolar electrode catheters and 1 tripolar electrode catheter were introduced from 1 or both femoral veins and from a left antecubital vein. The tripolar catheter was used to record His bundle electrograms. One quadripolar catheter was positioned at the high lateral right atrium for stimulation and recording of high right atrial electrical activity. One quadripolar catheter was positioned at the apex of the right ventricle for stimulation and recording of right ventricular activity. The third quadripolar electrode catheter was used for recording and stimulation of the proximal and distal coronary sinus. All intracardiac electrocardiograms were recorded using a filter setting of 40 to 1,000 cycles/s. The intracardiac electrograms and lead II were recorded using a 6-channel Mingograph recorder with paper speeds between 25 and 200 mm/s.

Anterograde refractory periods of the AV node and accessory pathways were determined using the extrastimulus technique[8,9] at an atrial pacing interval of 500 ms (programmed atrial pacing). High rate atrial pacing was performed starting at an atrial pacing rate of 120 beats/min and gradually increasing the rate by approximately 10 beats every 15 seconds until block occurred in the accessory pathway (Fig. 1).

The right ventricular effective refractory period was determined using the extra stimulus technique at a basic pacing interval of 500 ms (programmed ventricular pacing). Incremental high rate ventricular pacing was performed starting at a pacing rate of 120 beats/min and increasing the rate by approximately 10 beats every 15 seconds up to a rate of 200 to 250 beats/min depending on the patient's clinical state or until ventriculoatrial block occurred. During programmed and incremental ventricular pacing, retrograde atrial conduction was carefully assessed.

During the anterograde and retrograde pacing studies, the ability to induce sustained supraventricular tachycardia and the cycle length of the induced tachycardia were noted. Retrograde accessory pathway conduction during supraventricular tachycardia was established by the presence of abnormal (eccentric) retrograde atrial activation and by the ability to prematurely capture the atria during supraventricular tachycardia with critically timed ventricular extra stimuli delivered when the His bundle was refractory.[10] Location of the accessory pathway was based on determination of the earliest site of retrograde atrial activation during supraventricular tachycardia and on analysis of the initial QRS vector of maximally preexcited beats during sinus rhythm or atrial pacing.[11]

Atrial fibrillation: Atrial fibrillation was not deliberately induced in this study; however, when arrhythmia occurred as a result of the pacing techniques, 12-lead electrocardiograms were recorded and the shortest interval between successive beats showing preexcitation (shortest R-R interval) and the average R-R interval over a 1 minute period were measured.

Verapamil administration: After control measurements were made, intravenous verapamil (dose 0.15 mg/kg) was given over a 5 minute period and the same electrophysiologic measurements were then repeated.

Definitions: The anterograde effective refractory period of the accessory pathway was defined as the longest atrial coupling interval (A_1–A_2) at which block occurred in the accessory pathway (disappearance of the delta wave).[8] Accessory pathway refractory periods were measured from the same site before and after administration of verapamil. The site was as close as possible to the accessory pathway.[8]

Maximal 1:1 AV conduction through the accessory pathway to incremental high rate atrial pacing was defined as the

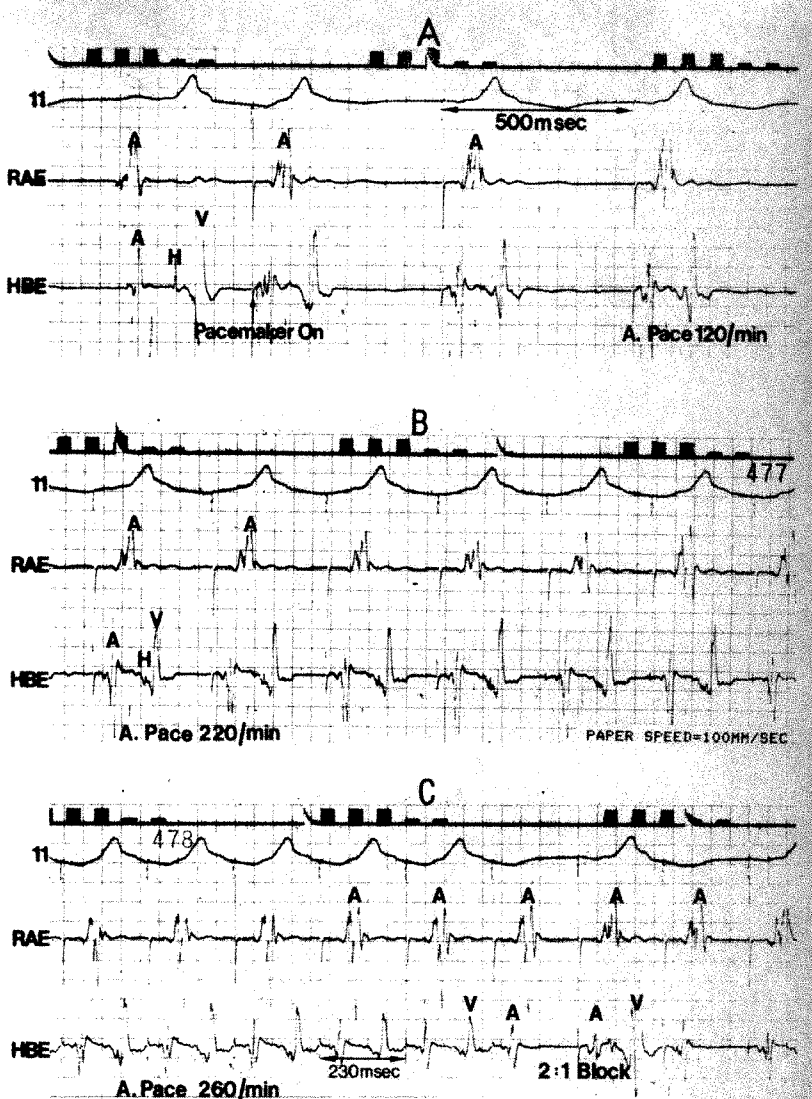

FIGURE 1. Technique of incremental high rate atrial pacing. **A,** commencement of atrial pacing at a rate of 120 beats/min. The first beat is a sinus beat with an abbreviated H-V interval due to preexcitation. **B,** atrial pacing has been increased to 220 beats/min with continued 1:1 conduction through the accessory pathway. **C,** at an atrial pacing rate just in excess of 260 beats/min (**arrow**), 2:1 block occurs in the accessory pathway. In this case, maximal 1:1 AV conduction through the accessory pathway is therefore 260 beats/min. In each panel, lead II, intracavity right atrial electrogram (RAE), and His bundle electrogram were recorded simultaneously. A = atrial activity; A.Pace = atrial pacing; H = His bundle activity; V = ventricular activity.

highest atrial pacing rate at which 1:1 anterograde (AV) conduction occurred through the accessory pathway. In our laboratory the coefficient of variation for duplicate measurements of this parameter is 2.1%.

The retrograde effective refractory period of the accessory pathway was defined as the longest ventricular coupling interval (V_1–V_2) at which the premature ventricular beat (V_2) failed to conduct to the atria through the accessory pathway.[8]

Maximal 1:1 ventriculoatrial (VA) conduction through the accessory pathway to incremental high rate ventricular pacing was defined as the highest ventricular pacing rate at which 1:1 VA conduction occurred through the accessory pathway.

Statistical analysis: Statistical analysis was performed using the 2-tailed *t* test for paired differences and 2-way analysis of variance.

Results

Anterograde properties of the accessory pathway (Table I): *The anterograde effective refractory period of the accessory pathway* could be measured in 9 of the 12 patients. In the remaining 3 patients (Patients 1, 2, and 8) atrial refractoriness precluded this measurement. The effective refractory period of the accessory pathway ranged from 220 to 310 ms (mean 283 ± 8 ms) during the control period and from 210 to 305 ms (mean 283 ± 10 ms) after the administration of verapamil (difference not significant [NS]).

Maximal 1:1 AV conduction through the accessory pathway to incremental high rate atrial pacing (Table I, Fig. 2) ranged from 180 to 290 beats/min (mean 227 ± 10) during the control period and from 170 to 330 beats/min (mean 258 ± 14) after the administration of verapamil ($p < 0.001$). Ten of the 12 patients showed an increase in maximal 1:1 AV conduction through the accessory pathway after verapamil. A typical response is shown in Figure 3. One patient (Patient 11) showed a decrease of 10 beats/min and 1 patient (Patient 4) had no change. The magnitude of the increase after verapamil tended to be greater in patients with the higher initial control values for this variable (Fig. 2).

Retrograde properties of the accessory pathway (Table I): Retrograde conduction through the accessory pathway could be demonstrated in 11 of the 12 patients

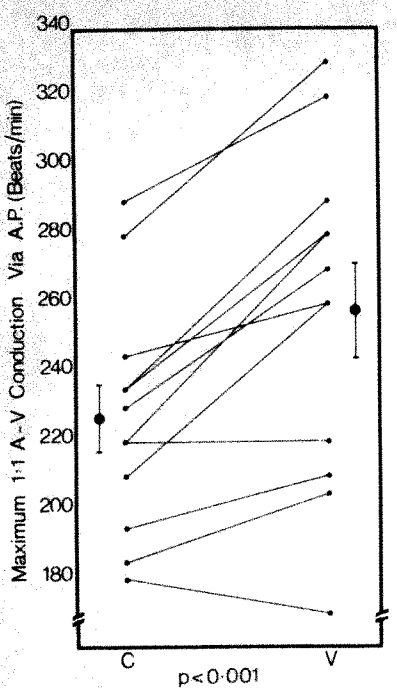

FIGURE 2. Effects of verapamil in each of the 12 patients on maximal 1:1 AV conduction through the accessory pathway during incremental high rate atrial pacing. Control (C) values are shown on the **left**, post-verapamil (V) values on the **right**. Mean values and standard error of the mean are shown. A.P. = accessory pathway.

before and after verapamil; no retrograde conduction could be demonstrated in Patient 9. The retrograde effective refractory period of the accessory pathway could be measured in only 4 patients (Table I). In the remaining 7 patients the functional ventricular refractory period exceeded the effective retrograde refractory period of the accessory pathway. In the 4 patients in whom this measurement could be obtained the mean control value was 258 ± 7 ms and the value after verapamil 253 ± 8 ms (NS).

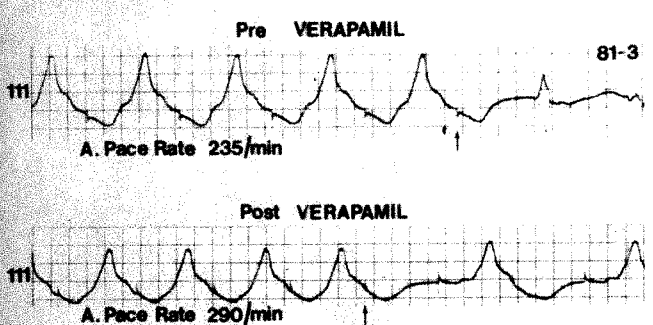

FIGURE 3. Patient 6. Typical effect of verapamil on maximal 1:1 AV conduction through the accessory pathway. The control value for this variable is 235 beats/min. At a slightly faster atrial pacing rate, block occurs in the accessory pathway (**arrow**) and a supraventricular beat due to exclusive conduction through the AV node ensues. Post verapamil, maximal 1:1 AV conduction through the accessory pathway increases to 290 beats/min. At a slightly faster atrial pacing rate, 2:1 block in the accessory pathway (**arrow**) occurs. III = lead III.

In 9 of the 11 patients retrograde conduction through the accessory pathway occurred during incremental high rate ventricular pacing up to the maximal tested rates (200 to 250 beats/min) (Table I). In 1 patient (Patient 3) the maximal rate of retrograde conduction through the accessory pathway increased from a control value of 205 to the highest tested rate of 220 beats/min after verapamil. In another patient (Patient 12) the rate increased from a control value of 235 to the maximal tested rate of 250 beats/min after verapamil.

Supraventricular tachycardia (Table I): Sustained supraventricular tachycardia could be induced by programmed pacing in 11 of the 12 patients before verapamil but in only 6 patients after verapamil. Ten of the 11 patients exhibited a typical "orthodromic" circus movement tachycardia with anterograde conduction through the AV node and His bundle and retrograde conduction through the accessory pathway.[11,12] One patient (Patient 7) exhibited both orthodromic supraventricular tachycardia and "antidromic" circus movement tachycardia.[11,12] In the latter instance, anterograde conduction occurred through the accessory pathway and retrograde conduction through the His bundle and AV node. After verapamil, supraventricular tachycardia could only be induced in 6 patients (Table I). In those 6 patients the tachycardia cycle length varied from 295 to 430 ms (mean 330 ± 20) before verapamil, and after verapamil the cycle lengths varied from 320 to 465 ms (mean 369 ± 21) ($p < 0.02$). The longer cycle lengths after verapamil reflected an increase in AV nodal conduction time (increase in A-H interval).

Atrial fibrillation (Table II): Atrial fibrillation resulted from high rate atrial pacing in 2 patients during the control period (Patients 5 and 8) and in 5 patients after verapamil (Patients 2, 5, 7, 8, and 9). In all instances atrial fibrillation occurred after a short period of block in the accessory pathway (Fig. 4). In cases 5 and 8 atrial fibrillation induced during the control period reverted spontaneously to sinus rhythm without drug therapy or electrical reversion. After verapamil, however, Patients 5, 8, and 9 required electrical reversion to restore sinus rhythm.

In Patients 2 and 9 in whom atrial fibrillation only occurred after verapamil, previously documented epi-

TABLE II Findings in Atrial Fibrillation*

	Atrial Pacing		Atrial Fibrillation			
	Shortest R-R 1:1 Conduction		Shortest R-R Interval		Average R-R Interval	
Case	C	V	C	V	C	V
2	260	220	240†	220	300†	273
5	260	215	250	200	333	250
7	255	215	. . .	210	. . .	261
8	205	190	180	165	273	240
9	305	285	280†	250	400†	364

* All measurements are given in milliseconds. † Value obtained during episode of atrial fibrillation before electrophysiologic study. C = control; V = verapamil.

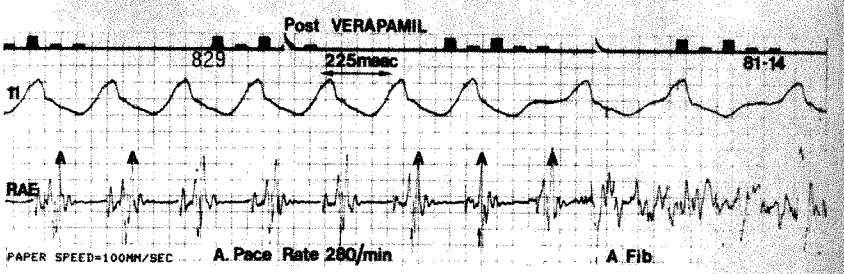

FIGURE 4. Patient 5, after verapamil. Induction of atrial fibrillation (A Fib) during incremental high rate atrial pacing. At an atrial pacing rate just in excess of 280 beats/min, a short period of 2:1 block in the accessory pathway (**arrow**) occurs and is followed by atrial fibrillation. Abbreviations as in Figure 1.

sodes of atrial fibrillation that had occurred when the patients were receiving no drug therapy were used for comparison with the postverapamil results. In the remaining case (Patient 7) in which atrial fibrillation only occurred after verapamil, no previous electrocardiogram during atrial fibrillation was available for comparison. Nine episodes of atrial fibrillation were therefore available for analysis. In all cases conduction during atrial fibrillation occurred exclusively or predominantly through the accessory pathway.

The average and the shortest R-R intervals during atrial fibrillation and after verapamil are shown in Table II. In these 5 patients the shortest R-R intervals during atrial pacing at which 1:1 AV conduction occurred through the accessory pathway are also shown in Table II. This latter measurement corresponds to the maximal atrial pacing rate at which 1:1 AV conduction occurred through the accessory pathway.

In the 4 patients in whom episodes of atrial fibrillation could be compared before and after verapamil, the average and the shortest R-R intervals were always shorter after verapamil (Table II). The mean average R-R interval was 327 ± 27 ms before and 282 ± 28 ms after verapamil ($p < 0.05$). The mean shortest R-R interval was 237 ± 21 ms before and 209 ± 18 ms after verapamil ($p < 0.05$). An example of atrial fibrillation before and after verapamil is shown in Figure 5.

A comparison between the shortest R-R intervals (y) during the 9 episodes of atrial fibrillation and the shortest R-R interval (x) at which 1:1 AV conduction occurred through the accessory pathway during incremental atrial pacing is shown in Figure 6. The correlation between these 2 variables was strong ($r = 0.95$). The regression equation was $y = 0.97x - 8.74$.

Discussion

Supraventricular tachycardia: The most common arrhythmia in patients with the Wolff-Parkinson-White syndrome is a paroxysmal circus movement (reentrant) tachycardia involving anterograde conduction through the AV node His bundle system and retrograde conduction through the accessory pathway (orthodromic supraventricular tachycardia).[11] Drugs such as verapamil that increase AV node refractoriness can terminate such arrhythmias and perhaps prevent their occurrence. Numerous investigators have demonstrated the effectiveness of an intravenous injection of verapamil in terminating spontaneous or induced episodes of supraventricular tachycardia.[1–5] Termination usually occurs as a result of block in the anterograde limb of the reentrant circuit (AV node).[1–5]

Recent reports suggest that the electrophysiologic response to acute intravenous drug administration accurately predicts the future response to oral adminis-

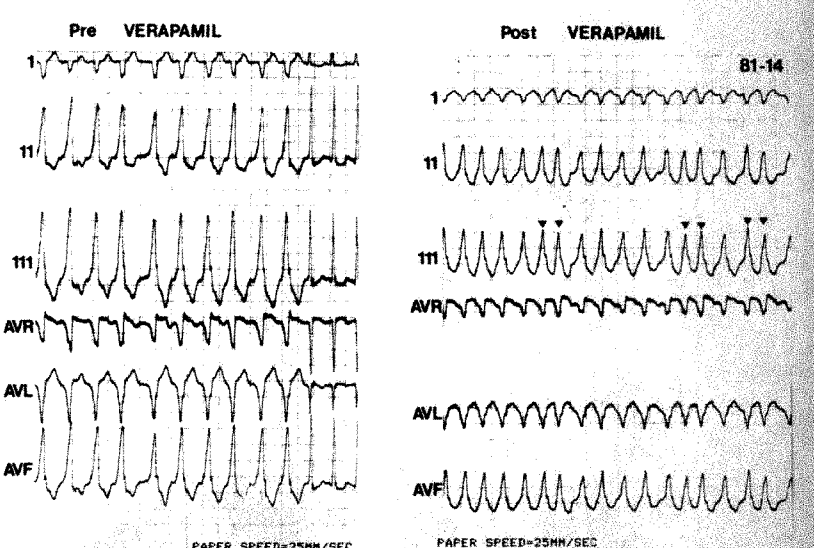

FIGURE 5. Patient 5. Six-lead electrocardiogram during atrial fibrillation before and after verapamil. The 6 leads are recorded simultaneously. The postverapamil electrocardiogram is recorded at half standard calibration. Note that post verapamil the average ventricular response is 240 beats/min, with all beats showing evidence of preexcitation. Several R-R intervals (**arrows**) are 200 ms in duration. Before verapamil the average ventricular response is 180 beats/min and some beats show exclusive conduction through the AV node.

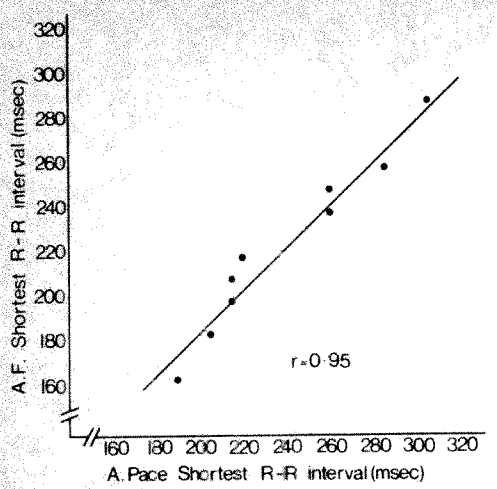

FIGURE 6. Relation between the shortest R-R interval during atrial fibrillation and the shortest R-R interval with 1:1 AV conduction through the accessory pathway during incremental high rate atrial pacing (A.Pace). Data from 9 episodes of atrial fibrillation are shown. The regression line is indicated.

tration of the same drug.[13] Some recent data suggest that this supposition may also be true for verapamil.[14] In our study it was still possible with programmed stimulation to induce episodes of supraventricular tachycardia in 6 of the 11 patients after a conventional dose of intravenous verapamil, although the tachycardia was invariably slower and sometimes terminated spontaneously. Of the 7 patients in whom orthodromic supraventricular tachycardia was the presenting problem, it was still possible to induce the tachycardia in 5 after intravenous verapamil. These results are similar to those reported by other investigators. Wellens et al[15] were still able to induce supraventricular tachycardia after intravenous verapamil in 3 of 3 patients with accessory pathways. Rinkenberger et al[5] were able to induce supraventricular tachycardia in 4 of 6 patients with the Wolff-Parkinson-White syndrome after intravenous verapamil.

The apparent discrepancy between the ability of verapamil to terminate an episode of supraventricular tachycardia and its inability to always prevent further induction of this arrhythmia is presumably related to differences between the immediate and the steady state effects of the drug. By producing an abrupt increase in AV node refractoriness, intravenous verapamil results in a sudden block in the AV node and therefore termination of the supraventricular tachycardia. Once a new equilibrium has been achieved in the AV node, it is often still possible to induce reentrant supraventricular tachycardia, albeit at a slower rate because of increased conduction time through the AV node.

On the basis of the acute results of this and other studies,[5,15] it seems likely that oral verapamil, when given alone in conventional doses, will not prevent episodes of supraventricular tachycardia in many patients with symptomatic Wolff-Parkinson-White syndrome.

Atrial fibrillation: When atrial fibrillation occurs in the Wolff-Parkinson-White syndrome, the ventricular response is largely determined by the anterograde properties of the accessory pathway.[16–20] If the refractory period is short, the ventricular response will be rapid and hemodynamic embarrassment or even ventricular fibrillation may occur.[11,21] Studies show that the risk of ventricular fibrillation is greatest when the mean ventricular response is fast and when the shortest interval between successive beats is 200 ms or less.[11,20] Drugs such as digoxin which sometimes shorten the refractory period of the accessory pathway may increase the risk of ventricular fibrillation.[20–23]

In this study verapamil significantly increased the maximal 1:1 AV conduction through the accessory pathway to incremental high rate atrial pacing in 10 of the 12 patients by an average of 31 beats/min. This effect of verapamil was more pronounced in patients with relatively fast control values for this variable. In 4 patients in whom episodes of atrial fibrillation could be compared, the ventricular response was always faster and the shortest R-R interval always shorter after verapamil. The foregoing findings strongly suggest that verapamil is likely to increase the ventricular response to spontaneous atrial fibrillation in patients with the Wolff-Parkinson-White syndrome and in some the consequences could be dangerous. Other investigators have reported similar findings.[5,7,24] Henning et al[7] reported on 7 patients with the Wolff-Parkinson-White syndrome and predominant conduction through the accessory pathway in whom verapamil increased the ventricular response to induced atrial fibrillation by an average of 30 beats/min and decreased the shortest R-R interval from a mean of 237 ms to a mean of 199 ms. Gulamhusein et al[24] reported that verapamil increased the ventricular response to induced atrial fibrillation in 4 of 8 patients with the Wolff-Parkinson-White syndrome. These investigators noted that patients with predominantly preexcited QRS complexes during atrial fibrillation appeared more likely to have acceleration of ventricular response than patients with predominantly normally conducted QRS complexes.

It could be argued that verapamil might prevent episodes of atrial fibrillation in patients with the Wolff-Parkinson-White syndrome either by altering the electrophysiologic properties of atrial muscle or by preventing or reducing the rate of reentrant supraventricular tachycardia. If this were so then the findings in this study would be of academic rather than practical significance. To our knowledge, however, there have been no studies that have specifically addressed this problem nor is there convincing evidence that verapamil prevents atrial fibrillation in other conditions associated with this arrhythmia. In our study atrial fibrillation during incremental high rate atrial pacing occurred more frequently after verapamil than during control measurements, but this probably was a reflection of the faster atrial pacing rates achieved after verapamil rather than any tendency of the drug to precipitate this arrhythmia. An associated observation was that both

episodes of atrial fibrillation during the control period reverted spontaneously whereas 3 of the 5 episodes after verapamil required electrical cardioversion. Similar findings were noted by Gulamhusein et al.[24] Until further information is available it would seem prudent to consider that verapamil may not prevent episodes of atrial fibrillation in patients with the Wolff-Parkinson-White syndrome and is likely to increase the ventricular response through the accessory pathway should this arrhythmia occur.

Possible mechanisms whereby verapamil could affect conduction of atrial impulses through the accessory pathway: Several mechanisms are possible. First, the drug could exert a direct effect on the cells of the accessory pathway. In the cat atria, verapamil decreases the action potential duration and increases the conduction velocity to rapid stimuli.[25] Hasin and Rogel[26] showed that verapamil slightly increases conduction velocity in the ventricular myocardium of the dog. If, as it seems likely, the accessory pathway is made up of either atrial or ventricular myocardium, verapamil could be expected to exert a similar effect and thus facilitate conduction.

A second means by which verapamil could indirectly influence anterograde conduction through the accessory pathway is its effect on the AV node. By slowing or blocking conduction of atrial paced beats or atrial fibrillation impulses in the AV node,[27] verapamil could reduce the degree of concealed retrograde penetration of the accessory pathway and thereby decrease anterograde refractoriness. A similar mechanism has been postulated to explain the increased ventricular response to atrial fibrillation after digoxin[22,23] in some patients with the Wolff-Parkinson-White syndrome.

Third, verapamil, by reducing blood pressure, may have reflexly increased sympathetic tone and thereby possibly altered conductivity and refractoriness of the accessory pathway.[28] Although both intravenous and oral verapamil will cause vasodilation and reduction of blood pressure, the effects of intravenous verapamil on sympathetic tone may be more pronounced than those of oral verapamil. We are therefore unable to say whether oral verapamil would have the same effects as intravenous verapamil on the ventricular response in atrial fibrillation.

Relation between refractory period estimation and response to high rate atrial pacing: An important finding in this study is that the effect of verapamil on the response to high rate atrial pacing could not have been predicted by the anterograde refractory period estimation of the accessory pathway. In this study, as in the study of Spurrell et al,[6] verapamil had no significant effect on the anterograde refractory period of the accessory pathway as determined by the extra stimulus technique. There are several possible reasons for the apparent discrepancy between the results of the refractory period estimation and the results of incremental high rate atrial pacing. Refractoriness of cardiac tissue is strongly influenced by heart rate.[29] A refractory period estimation at a pacing rate of 120 beats/min, as in this study, may not necessarily predict the refractory period response at atrial pacing rates of 200 beats/min or more. Furthermore, it is often impossible to estimate the anterograde effective refractory period of the accessory pathway because this determination may be limited by refractoriness of the atrial muscle,[8,11,20] as was the case in 3 of our patients. Finally, estimation of the effective refractory period may be influenced by relative differences in intraatrial conduction between the basic paced beat and the premature beat.[8,11] By altering atrial conduction, the true effects of a drug on the refractory period of the accessory pathway may be masked.[8,11] This problem will be minimized but not necessarily completely prevented by recording atrial electrograms close to the presumed site of the accessory pathway. In several studies the correlation between the accessory pathway refractory period and the shortest R-R interval during atrial fibrillation was relatively weak.[20,30]

In view of these difficulties with refractory period estimation, we believe that incremental high rate atrial pacing, which more closely simulates atrial flutter and fibrillation, is a preferable means of determining the likely effect that a drug will have on these tachyarrhythmias in patients with the Wolff-Parkinson-White syndrome. In our study there was a strong correlation between the shortest R-R interval achieved during atrial pacing and the shortest R-R interval during atrial fibrillation with a tendency for the former measurement to slightly overestimate the latter.

Clinical implications: The results of this study suggest that verapamil is likely to be of limited value in preventing episodes of supraventricular tachycardia in patients with the Wolff-Parkinson-White syndrome. More importantly, the drug may possibly increase the ventricular response to spontaneous atrial fibrillation with potentially dangerous consequences in patients who already have a fast response. For these reasons we believe that long-term verapamil therapy should be avoided in patients with the Wolff-Parkinson-White syndrome unless an electrophysiologic study has demonstrated its safety. The findings in this study do not detract from the usefulness of intravenous verapamil in terminating episodes of supraventricular tachycardia, providing the drug is administered under appropriate cardiac monitoring.

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Atrial Excitability and Conduction in Patients With Interatrial Conduction Defects

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Prolongation of P-wave duration is an accepted indicator of an interatrial conduction disturbance and may predispose patients to atrial arrhythmias. This study was performed to monitor electrophysiologic characteristics of the atria in patients with a prolonged P-wave duration. Atrial excitability and conduction times were compared in 7 patients with a P-wave duration <115 ms (Group I) and 13 patients with a duration ≥115 ms (Group II). In contrast to the Group I patients, most of the 13 patients in Group II had atrial arrhythmias, including sinus nodal dysfunction (3 patients) and a history of atrial fibrillation or ectopic atrial tachycardia (6 patients). Electrophysiologic differences between the 2 groups included a higher late diastolic threshold in Group II (0.8 ± 0.2 mA versus 1.3 ± 0.2 mA; p <0.005), and a greater increase in intraatrial conduction time (5 ± 10 ms versus 30 ± 20 ms; p <0.005) and interatrial conduction time (5 ± 15 ms versus 30 ± 15 ms; p <0.05) of early premature responses. There were no differences between the 2 groups in refractory periods, shape of the strength interval curve, or conduction times of premature responses occurring late in diastole.

These abnormalities in conduction time and excitability found in patients with a prolonged P-wave duration may predispose to the initiation of certain atrial tachyarrhythmias.

Human atrial tissue taken from patients with an enlarged atrium and a history of atrial tachyarrhythmias demonstrates abnormalities of the action potential that could, and probably would, alter conduction and excitability of the atrium, and create vulnerability to reentrant arrhythmias. Resting membrane potential is elevated, and the maximal amplitude of the action potential and upstroke velocity is depressed.[1-9] Given these known cellular abnormalities, we should be able to detect abnormalities in conduction and excitability in similar patients by standard endocardial extrastimulus pacing and recording techniques.

We report herein the results of clinical electrophysiologic studies of the intact human atrium designed to detect such abnormalities in patients with atrial disease. We classified our patients on the basis of the P-wave duration on the electrocardiogram and compared atrial excitability and conduction time in patients with normal and prolonged P-wave durations. We looked particularly for differences in conduction time of premature atrial responses in patients with a prolonged P-wave duration that might explain the propensity of early premature atrial beats to act as a trigger for the initiation of repetitive atrial beats or atrial fibrillation.

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Methods

Twenty consecutive patients, 11 men and 9 women aged 28 to 84 years who were in sinus rhythm, were studied. Cardioactive drugs were discontinued at least 72 hours before the procedure, and informed consent was obtained. The research procedure followed a clinical electrophysiologic study performed to evaluate sinus nodal dysfunction, atrioventricular conduction disturbances, supraventricular arrhythmias, or ventricular arrhythmias. Seven patients had atherosclerotic heart disease, 5 had hypertensive cardiovascular disease, and 1 had primary myocardial disease. Seven patients had no obvious organic heart disease. All patients with organic heart disease were in New York Heart Association[10] class I or II for congestive failure.

The patients were classified into 2 groups depending on the P-wave duration. The P wave was the average duration of 10 consecutive sinus beats from lead II of the electrocardiogram recorded during the electrophysiologic study at a paper speed of 250 mm/s. The P-wave duration and the appropriateness of the classification of each patient into Group I or II was confirmed by measuring the maximal duration of the P wave with vernier calipers from the standard electrocardiogram, magnified approximately 2.5 times by projection on an opaque screen.

In 7 patients the P-wave duration was <115 ms. These patients comprised Group I. In 13 patients, the P-wave duration was ≥115 msec. These patients comprised Group II. There was no significant difference between the 2 groups in sex distribution or in the type of underlying organic heart disease. Although the incidence of symptomatic congestive heart failure was greater in Group II, this difference did not achieve significance. Patients in Group II tended to be older (p <0.05) and to have undergone the electrophysiologic study for evaluation of sinoatrial or atrioventricular conduction abnormalities (p <0.06) (Table I).

TABLE I Clinical Characteristics

	Group I P<115 ms (7 Patients)	Group II P ≥115 ms (13 Patients)
Age (yr)	53 ± 16	65 ± 13
Organic heart disease	5	8
NYHA functional class II	1	5
Reason studied		
SA or AV block	2	10
SVT	2	2
VT	3	1

AV = atrioventricular; NYHA = New York Heart Association; SA = sinoatrial; SVT = supratricular tachycardia; VT = ventricular tachycardia.

Atrial excitability and conduction during early and late diastole were measured by the endocardial extrastimulus technique. Standard quadripolar catheters with an interelectrode separation of 1 cm were positioned in the high lateral right atrium by way of the right femoral vein. Atrial pacing was performed through the distal pair of electrodes and local atrial activation was recorded through the proximal pair of electrodes. In 16 patients catheters were positioned in the low septal right atrium to record a His bundle deflection. Left atrial activity was measured from the distal coronary sinus in 7 patients, the pulmonary artery in 2 patients, the lateral left atrium in 1 patient, and the mid-coronary sinus in 1 patient.[11] Since we were primarily interested in observing the change in conduction time of early compared with late premature atrial beats rather than in measuring conduction times to specific left atrial recording sites, and since each patient served as his (or her) own control, we treated these multiple left atrial recording sites as a single one (A_{LA}) in our analysis. The intracardiac electrograms were filtered through a band of 50 to 500 Hz.

The position of the high right atrial catheter was adjusted under fluoroscopy until a late diastolic threshold of <1 mA was obtained. If this could not be accomplished despite multiple changes in position and stimulus polarity, the catheter position and polarity that allowed the lowest stable late diastolic threshold was used. A stimulator designed by M. Bloom and Associates (Philadelphia, Pennsylvania) or one designed in our laboratory,[12] provided the drive (S_1) and premature (S_2) stimuli. The current strength of the stimulus was measured by a calibrated voltage-to-current converter and the voltage was displayed simultaneously with standard electrocardiographic leads I, II, and VI and with the intracardiac electrograms on a VR12 Electronics for Medicine recorder. Events were preserved on photographic paper at a speed of 100 to 250 mm/s and on magnetic tape for later review. The S_1 and S_2 stimuli were 2 ms in duration and were delivered from the same pair of electrodes. The current strength of the S_1 stimuli was held constant at twice the late diastolic threshold.

After 8 to 10 beats of drive pacing (S_1) at a cycle length of 600 ms (19 patients) or 500 ms (1 patient), a premature stimulus (S_2) was delivered. The current of the premature stimulus was decreased by 0.1 mA until it failed to induce a propagated response. The minimum current necessary to elicit a propagated atrial response was defined as the threshold at that S_1–S_2 coupling interval. The S_1–S_2 interval was decreased by 10 ms decrements during early diastole and the current of the S_2 increased as needed until a premature stimulus of 10 times the diastolic threshold failed to initiate a propagated response.

Definitions: The *effective refractory period* was defined as the longest S_1–S_2 interval at which a stimulus of 10 mA failed to initiate a propagated response. The *functional refractory period* was defined as the shortest attainable A_1–A_2 interval. The *total refractory period* was the S_1–S_2 interval at which the threshold assumed a steady level that was maintained for the remainder of the cardiac cycle. The *relative refractory period* was the difference between the effective and total refractory periods. The *late diastolic threshold* was the average threshold following the end of the total refractory period. These definitions were developed in previous experiments in man and in intact animals.[13]

Sinus echo beats were defined as spontaneous, premature A_3 responses having a P-wave configuration and activation sequence similar to the normal sinus beat and occurring before the line of interpolation.[14] *Repetitive atrial firing* was defined as 2 or more spontaneous atrial responses with an A_2–A_3 cycle ≤250 ms and subsequent A_3–A_4 cycles ≤300 ms.[15]

The conduction time from the S_2 stimulus to the first high amplitude, high frequency deflection of each of the recording catheters was measured at the threshold current for each S_1–S_2 interval. During the relative refractory period the amplitude and frequency of local electrograms tended to decrease in most patients. When this occurred, measurements were made to the first high frequency deflection that was reproducible on preceding and subsequent S_1–S_2 test intervals and clearly distinguishable from the baseline. The *intraatrial conduction time* (A_{HRA}–A_{HIS}) was obtained by subtracting the time delay of the stimulus artifact of the high right atrial electrogram (S–A_{HRA}) from the time delay of the stimulus to the low septal right atrial electrogram (S–A_{HIS}). The *interatrial conduction time* was measured in a similar manner using the left atrial and high right atrial electrograms (A_{HRA}–A_{LA}). Strength-interval and conduction-interval curves were constructed by plotting threshold current and conduction time as a function of S_1–S_2 or A_1–A_2 intervals.

The late diastolic threshold was measured from the high right atrial catheter at the beginning and the end of the strength-interval measurements. If catheter position changed or an unexpected change in threshold occurred, the catheter was repositioned and the study repeated.

The *maximal sinus nodal recovery time* was measured in 18 patients by the method described by Dhingra et al.[16]

Statistical methods: Differences between groups are expressed as the mean ±1 standard deviation. Significance was analyzed by the 2-sample *t* test, or by Fisher's exact test when appropriate.

The relation between conduction time and threshold was analyzed as a growth curve. For each patients, the threshold at all S_1–S_2 coupling intervals was normalized to the late diastolic threshold. The Mann-Whitney test was applied to the median conduction times of arbitrarily assigned overlapping intervals of the current threshold.

Results

Table II presents the P-wave duration, the late diastolic threshold, the maximal change in conduction time, and the arrhythmia history of each patient. Sinoatrial block or other electrocardiographic characteristics of the sick sinus syndrome[17] were present in 7 Group II patients and in 1 Group I patient. The sinus nodal recovery time was normal in all patients in Group I but was prolonged in 3 patients in Group II. Paroxysmal supraventricular tachycardia caused by reentry within the atrioventricular node in 2 patients in Group I, sustained atrial fibrillation in 5 patients in Group II, and ectopic atrial tachycardia in 1 patient in Group II had been documented before the study. No patient in

TABLE II P-Wave Duration, Diastolic Threshold, Change in Conduction Time and Atrial Arrhythmias

Patient	P-Wave Duration (ms)	Threshold (mA)	Maximal Increase (ms) in			Atrial Tachyarrhythmias	
			$S-A_{HRA}$	$A_{HRA}-A_{HIS}$	$A_{HRA}-A_{LA}$	Historical	Induced
			Group I				
1	105	1.2	85	0	...	0	0
2	110	0.7	75	0	0	0	0
3	100	0.6	30	25	...	0	0
4	105	0.9	70	0	0	0	0
5	105	0.9	75	...	25	0	Echo
6	105	0.6	45	5	...	0	0
7	105	0.6	45	0	0	0	0
			Group II				
8	140	1.3	95	...	35	0	Echo
9	160	1.3	50	...	20	AF, flutter	Echo
10	120	1.1	80	40	...	0	Echo
11	125	1.3	115	60	...	0	RAF
12	125	1.6	25	20	25	EAT	0
13	125	1.4	60	0	...	AF	0
14	120	1.1	70	15	...	AF	0
15	115	1.4	30	50	50	AF	0
16	120	1.1	40	10	...	0	Echo
17	140	1.1	30	30	20	AF	0
18	120	1.3	10	...	0	0	0
19	120	1.0	55	55	...	0	RAF
20	125	...	60	40	45	0	Echo

AF = atrial fibrillation; EAT = ectopic atrial tachycardia; ECHO = single sinus echo beat; RAF = repetitive atrial firing.

Group I had a history of atrial fibrillation, ectopic atrial tachycardia, or atrial flutter.

Refractory period, late diastolic threshold, and the atrial strength interval relationship: The effective, functional, total, and relative refractory periods of both groups were similar (Table III).

The late diastolic threshold was higher in patients in Group II (Fig. 1). Threshold increased at short S_1-S_2 intervals. For most patients, threshold increased continuously during the relative refractory period (Fig. 2). However, 1 patient in Group I and 3 patients in Group II demonstrated decreases of ≥20% below the late diastolic threshold before the effective refractory period. One additional Group II patient had an unexpected but less dramatic decrease in threshold that did not fall below the late diastolic value. This period when threshold was lower than in late diastole ranged from 25 to 125 ms and had a mean duration of 65 ± 30 ms.

We attributed this apparent "dip" in the excitability curve to stimulus polarity, since in each of 3 tested patients we were able to induce such a "dip" by reversing the polarity of the stimulating electrodes. In addition, reversing the polarity increased the late diastolic threshold by a small amount (0.2 to 0.3 mA) but did not change the effective refractory period and the intraatrial and interatrial conduction times.

TABLE III Refractory Periods

	Group I P <115 ms	Group II P ≥115 ms	p
Effective	235 ± 30	235 ± 45	NS
Functional	305 ± 25	295 ± 50	NS
Total	345 ± 45	345 ± 90	NS
Relative	105 ± 50	110 ± 55	NS

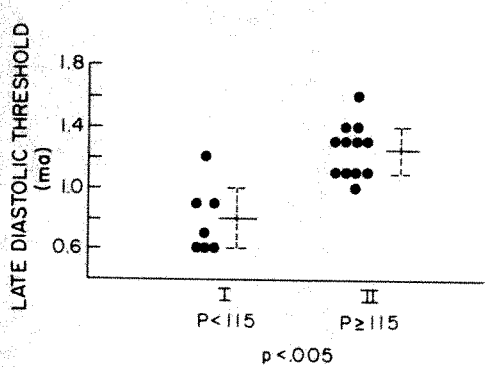

FIGURE 1. Late diastolic threshold in patients with a normal (Group I) and prolonged P-wave duration (Group II). The mean value in Group I was 0.8 ± 0.2 mA, with a range of 0.6 to 1.2. The mean value in Group II was 1.3 ± 0.2 mA, with a range of 1.0 to 1.6. This difference was significant ($p < 0.005$).

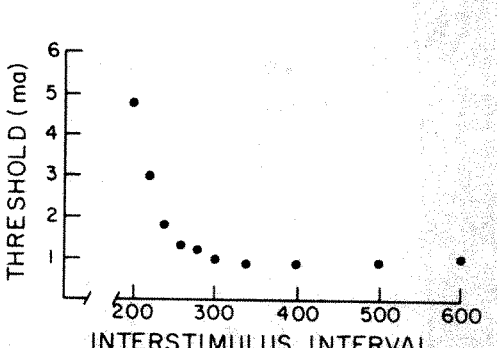

FIGURE 2. Atrial strength-interval curve from a patient from Group II with a P-wave duration of 118 ms. The interstimulus interval is the S_1-S_2 interval expressed in milliseconds.

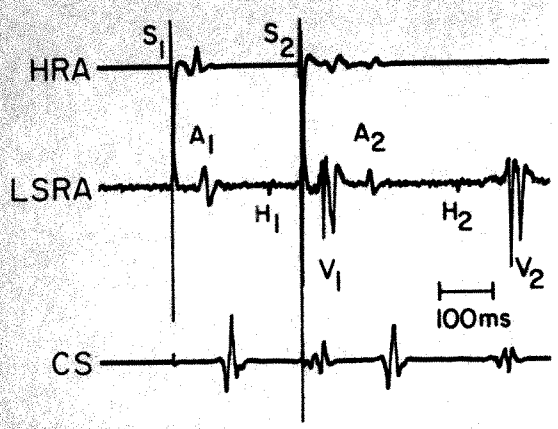

FIGURE 3. Intracardiac recordings from the high right atrium (HRA), low septal right atrium (LSRA), and distal coronary sinus (CS) in the patient discussed in Figure 2. At this S_1–S_2 coupling interval, the threshold has increased. The conduction time from the S_2 stimulus to the local electrograms of the HRA, LSRA, and CS catheters has increased, as have the conduction times from the local atrial electrogram of the HRA catheter to the local atrial electrograms of the LSRA and CS catheters. The paper speed was 100 mm/s. S_1 is the stimulus artifact of the nonpremature beat, A_1 is the response, H_1 is the His bundle deflection, and V_1 is the local ventricular electrogram. S_2, A_2, H_2, and V_2 refer to the premature response.

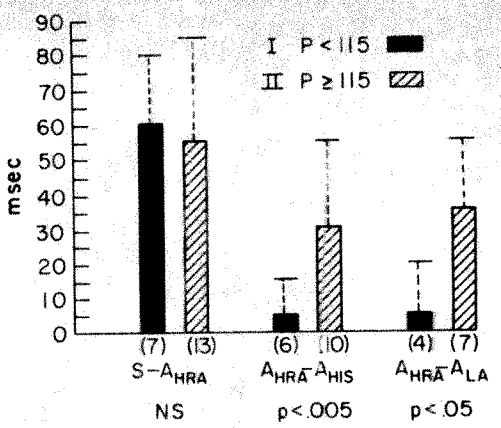

FIGURE 4. Maximal increase in latency (S–A_{HRA}), intraatrial (A_{HRA}–A_{HIS}), and interatrial (A_{HRA}–A_{LA}) conduction time of early premature responses induced during the relative refractory period. The intra- and interatrial conduction time increased significantly in Group II patients. There was no significant difference in S–A_{HRA} in the 2 groups. The **numbers in parentheses** represent the number of patients in whom the conduction time was measured.

Atrial conduction times of premature and nonpremature responses: For nonpremature responses or for premature responses induced at long S_1–S_2 coupling intervals, there was no significant difference in S–A_{HRA}, A_{HRA}–A_{HIS}, or A_{HRA}–A_{LA} for Groups I or II. However, a significant difference between the 2 groups developed as the S_1–S_2 interval was decreased and the relative refractory period was entered. This consisted of a greater increase in the intraatrial and interatrial conduction time in the Group II patients. Figure 3 is an example of the changes in conduction time of early atrial responses in a patient from Group II. During S_1–S_1 pacing, the conduction times are constant. During premature stimulation at short S_1–S_2 intervals, the S–A_{HRA}, A_{HRA}–A_{HIS}, and A_{HRA}–A_{LA} intervals increase.

Figure 4 shows the maximal increase in these conduction intervals of premature responses induced during the relative refractory period in all patients. S–A_{HRA} more than doubled in both groups, but there was no significant difference in the magnitude of the increase between the groups. In contrast, the increase in A_{HRA}–A_{HIS} and A_{HRA}–A_{LA} was significantly greater in Group II. Eleven of the 13 patients in Group II and 2 of the 7 patients in Group I had an increase >10 ms in interatrial or intraatrial conduction. Examples of the difference in early responses in the 2 groups are shown in Figure 5.

There was a direct correlation between the increase in intraatrial conduction time and the increase in interatrial conduction time. Seven patients had simultaneous measurements of both intraatrial and interatrial conduction. Stimulation at short S_1–S_2 intervals within the relative refractory period resulted in no change in either intraatrial or interatrial conduction in 3 patients,

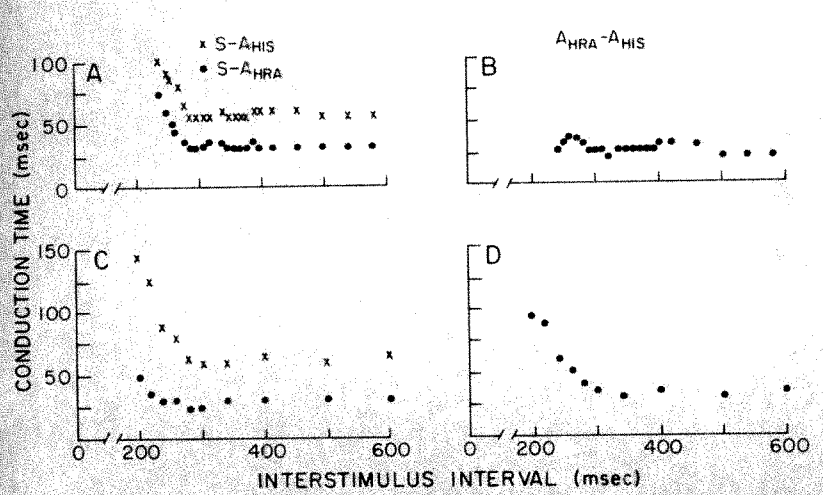

FIGURE 5. Examples of conduction-interval curves from 2 patients. **Panels A** and **B** are from a patient in Group I with a P-wave duration of 100 ms. **Panel A** is a graph of the conduction time from the stimulus to the local high right atrial electrogram (S–A_{HRA}) and from the stimulus to the local atrial electrogram of the low septal right atrial catheter (S–A_{HIS}). **Panel B** shows the intraatrial conduction time (A_{HRA}–A_{HIS}) determined by subtracting the latter 2 conduction intervals. As can be seen, there is little increase in A_{HRA}–A_{HIS}. **Panels C** and **D** are from the same patient described in Figure 2. A marked increase in intraatrial conduction time is seen.

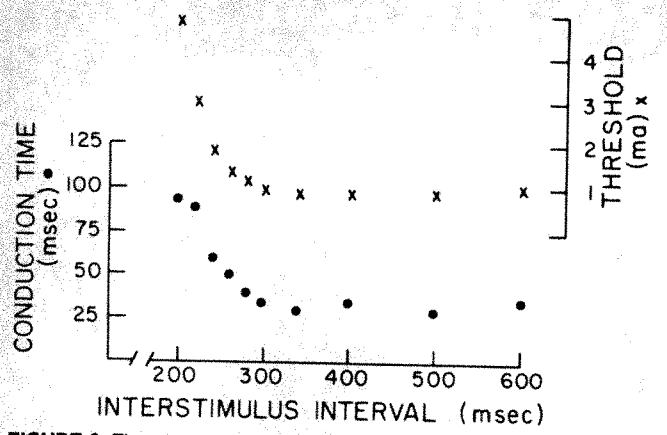

FIGURE 6. The strength-interval and conduction-interval curves from the patient described in Figure 2 are plotted on the same graph to show the simultaneous increase in intraatrial conduction time (A_{HRA}–A_{HIS}) and threshold.

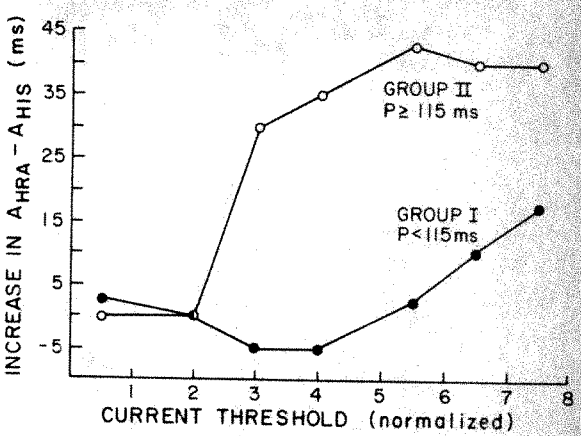

FIGURE 7. Relation of the increase in intraatrial conduction time (A_{HRA}–A_{HIS}) to threshold current. The threshold current was normalized by dividing the threshold at each S_1–S_2 interval by the late diastolic threshold for each patient. The points on the graph represent the change in the median conduction time plotted at the mid-point of intervals of the threshold current. Significant differences ($p < 0.01$) between the 2 groups in the change in conduction time are present at the mid-range of threshold currents.

a 50 ms increase in both conduction times in 1 patient, and a 20, 30, and 40 ms increase in intraatrial conduction associated with, respectively, a 25, 20, and 45 ms increase in interatrial conduction time in the 3 remaining patients. The correlation was significant (Spearman's $r = 0.96$, $p < 0.002$).

Relation between threshold and conduction time: Because of the difference in the conduction time of early premature responses in the 2 groups, the relation between threshold current and the increase in intraatrial and interatrial conduction also differed. In Group II, changes in conduction time tended to parallel the increase in threshold during the relative refractory period (Fig. 6). This did not occur in Group I. This difference in the relation between threshold current and intraatrial conduction is also shown in Figure 7.

To confirm that the increase in stimulus strength did not cause the increase in interatrial or intraatrial conduction, we tested the effect of a 2- to 3-fold increase in stimulus threshold during late diastole in 5 patients who demonstrated an increase in conduction time of the early premature response. This maneuver did not influence intraatrial or interatrial conduction time. Two of these patients had a small (10 ms) decrease in S–A_{HRA}.

Correlation with atrial arrhythmias: The ability to induce repetitive atrial firing or sinus echo beats was associated with the maximal increase in atrial conduction time ($p < 0.005$). Figure 8 illustrates the relation between the maximal conduction slowing in the premature response and the development of single or multiple spontaneous atrial responses. All 6 patients without conduction slowing in the premature response were in Group I. None had either single or multiple spontaneous response. The 2 patients with repetitive atrial firing had the greatest increase in interatrial conduction; both were in Group II. Five of the 6 patients with a >30 ms increase in intra- or interatrial conduction time had either repetitive atrial firing or sinus echo beats; the other patient had a history of recurrent lone atrial fibrillation. Figure 8 also shows that an increase in conduction time from 10 to 30 ms in the premature response was not predictive of a spontaneous response, since 4 of these patients had no such beats and 3 had only a single sinus echo beat.

All patients with either prolonged sinus node recovery times or a history of atrial fibrillation were in Group II. However, within this group there was no apparent correlation between the maximal increase in atrial conduction time, sinus nodal dysfunction, or the history of atrial fibrillation. There was no apparent correlation

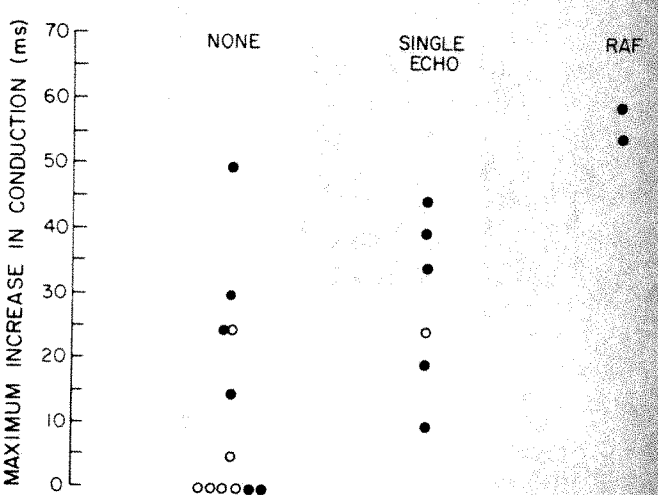

FIGURE 8. Relation between the change in intraatrial and interatrial conduction time and the initiation of single echo beats and repetitive atrial firing (RAF). Atrial conduction time refers to either intra- or interatrial conduction, depending on which measurement was available. If both conduction times were measured, the conduction time with the greatest change is shown. The **open circles** represent Group I patients and the **closed circles** Group II patients. The association between the increase in atrial conduction time and the induction of echo and repetitive atrial firing is significant ($p < 0.005$).

between historical atrial fibrillation and our ability to induce sinus echo beats or repetitive atrial firing.

Neither the shape of the atrial strength interval curve nor the duration of the atrial refractory periods was a correlate of induced echo beats or repetitive firing or of historical atrial fibrillation.

Discussion

Our results are consistent with those of single fiber studies performed in human atrial tissue removed at the time of cardiac surgery.[6–9] Fibers from the patients with an enlarged atrium, a prolonged P-wave duration, and a history of preoperative atrial arrhythmias had changes in the resting membrane potential, maximal velocity of the action potential upstroke, and the action potential amplitude, each of which are associated with depressed conduction velocity and depressed excitability.[6] These electrophysiologic abnormalities would explain the elevated late diastolic threshold we found in Group II patients. They are also consistent with the concept that a prolonged P-wave duration represents an interatrial conduction defect that can occur independently of an increase in atrial size.[18] The increased conduction slowing of the early premature response in our patients with interatrial conduction defects probably occurs because of further depression of conduction velocity of abnormal and already partly depressed atrial fibers.

However, although conduction slowing of early premature responses occurs primarily in the group with a prolonged P wave, the correlation between P-wave duration and conduction slowing of early premature responses was poor. Some patients with only slightly prolonged P-wave durations had a major increase in conduction time of early premature responses, while other patients with more marked P-wave durations had only minor increases in conduction time, It is unlikely that this apparent discrepancy reflects inaccurate measurement of P-wave durations since the P-wave duration was confirmed by 2 methods. Rather, it suggests that abnormalities in atrial conduction may exist in the absence of obvious changes of P-wave duration, and that a P wave >115 ms identifies patients with abnormalities in atrial conduction and excitability.

Previous studies of intact animal and normal human atria have demonstrated that atrial conduction times of very early premature beats may lengthen.[19–21] However, these studies did not attempt to separate the conduction slowing into that attributable to changes in latency occurring near the stimulating electrode and those caused by more distal conduction delays. This difference is important because changes in latency can be caused by changes in the strength of the stimulus and other factors. Increases in latency are not generally believed to be caused by depression of conduction velocity.[22]

Our study demonstrates that conduction time in patients with a diseased atrium and interatrial conduction defects during sinus rhythm may be further prolonged by premature stimulation during the relative refractory period. In our experiments $S–A_{HRA}$, which includes stimulus latency, increased in all of our patients and the amount of increase was similar in both the patients with a normal and prolonged P-wave duration. However, clear differences in intra- and interatrial conduction in the 2 groups of patients could be detected in the early atrial premature responses.

This difference in conduction time of the premature response is even more striking when seen in the light of the similarity in conduction time of the nonpremature beat in the 2 groups. We did not find the expected slightly longer inter- and intraatrial conduction times in the patients with prolonged P-wave durations, a fact that may be partly explained by the limitation of the P wave as a measurement of atrial conduction and, more importantly, by electrode positioning in our protocol. Being interested in the difference in conduction time of early and late premature beats, we did not attempt to measure the maximal intra- or interatrial conduction times. Catheters were positioned in the high right atrium to achieve stable, low, late diastolic thresholds, and a variety of left atrial positions were used to measure the interatrial conduction time. This procedure probably caused the distances between recording electrodes to be relatively short and variable from patient to patient. The methodology may have prevented us from detecting the expected difference in interatrial and intraatrial conduction of nonpremature beats between the 2 groups.

It is possible that the prolongation of conduction times may have been caused by a shift in atrial conduction pathway of early premature beats. However, the continuous increase in conduction time during the relative refractory period, the constancy of the atrial activation sequence, and the fact that both inter- and intraatrial conduction increased, and not one or the other, suggests that conduction slowing rather than a shift in pathway was responsible for the observed changes. Moreover, since atrial conduction for distances of up to several centimeters is believed to be radial from the point of stimulation, a shift in conduction pathway would be unlikely.[23–25] Neither the influence of the autonomic nervous system on atrial conduction nor the theoretical difficulty of measuring conduction independently of excitability, as outlined elsewhere,[22,26–28] can explain the increase in conduction time of early premature responses which we observed in the patients with diseased atria.

It is not surprising that some markers of atrial excitability were similar in patients with normal and prolonged P-wave durations. These markers included the duration of the atrial refractory periods and the shape of the atrial strength-interval curve (that is, the presence, magnitude, or duration of a decrease in threshold before the effective refractory period). Atrial refractory period varies with paced cycle length and electrode position and is probably not useful as a method of separating normal from disease atria.[29–31] Our observation, that a decrease in threshold could be introduced at short $S_1–S_2$ intervals by reversing the polarity of the pacing stimulus, suggests that anodal pacing is the primary cause of the enhanced excitability seen in our patients.

The finding of a large difference in the diastolic threshold of Group I and II patients was unexpected. The possible existence of differences in the geometry or size of the right atrium of Group II patients, causing poor electrode contact with the atrial wall, does not fully account for this finding. Catheter positions were stable in both groups. Nor can this difference in thresholds be explained by the bipolar configuration of the pacing electrodes. Both anodal and cathodal current can stimulate the heart, depending on which electrode is in better contact and which phase of repolarization the excitable tissue is undergoing.[22] The excitability curves of the 1 patient in Group I and 3 patients in Group II demonstrated a decrease in threshold at early S_1–S_2 intervals as seen in anodal strength interval curves. Since anodal stimulation may have a higher threshold in late diastole, we analyzed our results excluding these 4 patients and still found a significant difference in late diastolic threshold between the 2 groups ($p < 0.005$).

We believe this difference in diastolic threshold is evidence of the importance of excitability in determining conduction velocity in human atrial tissue. Single-fiber studies and experiments with intact animals have demonstrated a close relation between excitability and conduction velocity. Factors that increase the current required to induce a propagated response tend to slow conduction of the response, and some investigators consider excitability a major determinant of conduction velocity.[32] Our studies of human atria corroborate the association of depressed conduction with depressed excitability.

We expected patients with a history of atrial fibrillation to show a greater increase in atrial conduction time than patients without such a history. That this did not occur may be explained by several factors; of these, study design and patient selection may be most important. Further prospective studies specifically designed to test the correlation between slowed conduction of early atrial premature responses and atrial fibrillation are needed.

Conclusions: We found elevated late diastolic threshold and abnormal conduction of early premature atrial beats in a group of patients with a prolonged P-wave duration and a history of atrial arrhythmias. Our study suggests that repetitive atrial firing and sinus echo beats may occur in this group of patients because of slow conduction of early premature beats. The slowed conduction, coupled with the shortened refractoriness known to characterize early premature beats,[33] provides an ideal electrophysiologic substrate for reentry and development of these atrial tachyarrhythmias.

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Termination of Ventricular Tachycardia

Evaluation of a New Pacing Method

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Ventricular extrastimuli or rapid ventricular pacing used to terminate ventricular tachycardia (VT) may be ineffective or may accelerate VT. Therefore, a new method to facilitate termination of VT and decrease the incidence of acceleration was evaluated. The new method utilized rapid ventricular pacing at cycle lengths 10 to 100 ms shorter than VT cycle length with the introduction of 1 or 2 ventricular extrastimuli. The efficacy of this combination method in terminating VT was assessed in 25 patients in whom ventricular extrastimuli and rapid ventricular pacing at cycle lengths and coupling intervals comparable with those used in the new method were unsuccessful. This combination method successfully terminated VT in 21 of 25 patients with cycle lengths of 230 to 400 ms. VT was terminated in 6 of 8 patients receiving drugs in whom VT could not be terminated by 1 to 2 ventricular extrastimuli or rapid ventricular pacing; in 6 of 8 patients unresponsive to ventricular extrastimuli and in whom rapid ventricular pacing produced acceleration of VT; and in 9 of 9 patients in whom antiarrhythmic agents made VT unresponsive to ventricular extrastimuli or rapid ventricular pacing. A combination of rapid pacing and extrastimuli can terminate VT unresponsive to ventricular extrastimuli or rapid ventricular pacing alone and may avoid acceleration of VT using rapid ventricular pacing at very short cycle lengths for termination.

Programmed stimulation of the heart has permitted investigation of patients with recurrent ventricular tachyarrhythmias through induction of their arrhythmias, enabling assessment of specific drug therapy.[1–8] Termination of VT in the electrophysiology laboratory by pacing techniques has allowed these studies to be done with relative safety and minimal discomfort to the patient. Furthermore, termination procedures may be used as a guide for potential pacemaker therapy in patients with drug-resistant arrhythmias.[3,9–13] Successful termination of VT using implantable pacemakers has been described previously. These techniques, however, are not without risk.

Introduction of 1 or more premature extrastimuli during VT or rapid overdrive pacing may fail to terminate VT and, in some cases, results in acceleration of VT or degeneration to ventricular fibrillation, or both, requiring cardioversion or defibrillation.[3,4,9,10] Such occurrences increase the risk and discomfort to the patient, and limit the use of pacing as a therapeutic technique.

The reported incidence of acceleration of VT or degeneration to ventricular fibrillation varies from 7 to 50%; the latter figure is associated with very rapid overdrive pacing rates.[3,4,9,10] In an effort to improve our ability to terminate VT successfully and to reduce the incidence of acceleration, a new method of programmed stimulation combining overdrive pacing with premature stimulation was evaluated.

Methods

Patients: The study population included 25 patients who were undergoing electrophysiologic studies for the evaluation and management of recurrent sustained VT or who were

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survivors of cardiac arrest. There were 17 men and 8 women, aged 34 to 74 years. Twenty-one of the 25 had ischemic heart disease, all of whom had previous myocardial infarction and 16 of whom had left ventricular aneurysms. The site of infarction was anterior in 13 patients and inferior in 7. One patient had both anterior and inferior infarctions. The remaining patients had arrhythmogenic right ventricular dysplasia, idiopathic congestive cardiomyopathy, and mitral valve prolapse. Fourteen of the patients were taking antiarrhythmic agents at the time of the study.

In all patients, VT was inducible by programmed stimulation using previously reported methods.[1,8,9] In each of these patients, the tachycardia was stable enough so that the ability of single or multiple extrastimuli and rapid pacing as methods of terminating the tachycardia could be evaluated. The termination protocol was identical to our standard protocol.[1,8,9] A single premature stimulus was coupled to the right ventricular electrogram at progressively decreasing intervals until refractoriness was reached. If the tachycardia persisted, a second and occasionally a third extrastimulus was introduced in a similar fashion. If these methods failed to terminate tachycardia, asynchronous bursts of stimuli were given to ensure 6 to 10 captures. These bursts were delivered initially at cycle lengths 10 ms less than that of the tachycardia and progressively decreased by 10 to 25 ms decrements to 225 to 250 ms, or until acceleration of tachycardia occurred. In all instances, VT either could not be terminated or was accelerated by single, double, or triple extrastimuli or by rapid pacing. All stimulation was performed with a specially designed programmable stimulator (Bloom Associates, Narberth, Pennsylvania) using rectangular pulses 1 ms in duration at twice diastolic threshold.

The patients were divided into 3 groups based on response to stimulation during VT and the effects of antiarrhythmic agents. Although somewhat arbitrary, the separation of patients allows consideration of all the specific situations in which the combination method might be useful. There was no difference in mean VT cycle length among the groups. The first group included 8 patients (Cases 1 to 8, Table I) in whom premature stimuli and overdrive pacing were ineffective in terminating VT. A second group of 8 patients (Cases 9 to 16) included those in whom overdrive pacing resulted in acceleration of VT or degeneration of this rhythm to ventricular fibrillation. Five of these patients were taking antiarrhythmic agents at the time of the study. In all instances, the response of rapid pacing with the antiarrhythmic agents was identical to that seen before administration of the antiarrhythmic agents. A third well-defined group of patients included 9 patients (Cases 17 to 25) in whom premature stimuli or overdrive pacing had successfully terminated VT in the baseline state (that is, with no antiarrhythmic drugs present) but were ineffective in terminating VT after therapy with the antiarrhythmic agents listed in Table I.

Combination method protocol: After attempts to terminate tachycardia using the standard methods listed (Table I), a combination method, consisting of the introduction of 1 or more ventricular premature stimuli after 8 to 10 beats of overdrive pacing, was employed. Overdrive pacing was given as asynchronous bursts 10 to 100 ms faster than the VT cycle length and was identical to overdrive-paced cycle lengths that were ineffective in terminating tachycardia. The premature stimuli were delivered at coupling intervals previously shown incapable of terminating tachycardia by themselves. No systematic analysis of later or earlier stimuli was performed. An example of the combination method is shown in Figure 1. VT with a left bundle branch block pattern and a cycle length of 400 ms is not terminated by a single premature stimulus or rapid pacing. The combination of pacing and premature stimulus, at the same cycle length and coupling interval noted to be individually ineffective abruptly terminates tachycardia.

TABLE I Patient Population

Patient	Age (yr) & Sex	Heart Disease	Site of MI	Site of Aneurysm	Arrhythmia	Drugs
1	62M	IHD	INF	INF	RVT	...
2	60M	IHD	INF	...	RVT	...
3	74F	IHD	ANT	ANT	RVT	...
4	34M	RVD	...	...	RVT	...
5	65M	IHD	ANT	ANT	RVT	...
6	65M	IHD	ANT	ANT	RVT	...
7	45F	IHD	IMI	...	RVT	...
8	52M	IHD	ANT	ANT	RVT	...
9	66F	IHD	IMI	...	CA-VF	Disopyramide phosphate
10	57M	IHD	ANT	ANT	RVT	...
11	41M	IHD	ANT	ANT	CA-VF	...
12	63M	IHD	INF	...	RVT	Procainamide
13	62M	CM	...	...	RVT	Procainamide
14	63F	MVP	...	...	RVT	Aprindine
15	54M	IHD	ANT	ANT	RVT	Quinidine
16	56M	IHD	ANT	ANT	RVT	...
17	56F	IHD	ANT	ANT	CA-VF	Quinidine
18	62F	IHD	ANT	ANT	RVT	Procainamide
19	54M	AR	...	...	RVT	Quinidine
20	56M	IHD	ANT/INF	Apical	RVT	Amiodarone
21	49M	IHD	INF	...	RVT	Quinidine
22	62M	IHD	ANT	ANT	CA-VF	Quinidine
23	42F	IHD	INF	INF	RVT	Quinidine
24	57F	IHD	ANT	ANT	RVT	Procainamide
25	59M	IHD	ANT	ANT	RVT	Procainamide

ANT = anterior wall; AR = aortic regurgitation; CA-VF = cardiac arrest-ventricular fibrillation; CM = cardiomyopathy; IHD = ischemic heart disease; INF = inferior wall; MVP = mitral valve prolapse; RVD = right ventricular dysplasia; RVT = recurrent ventricular tachycardia.

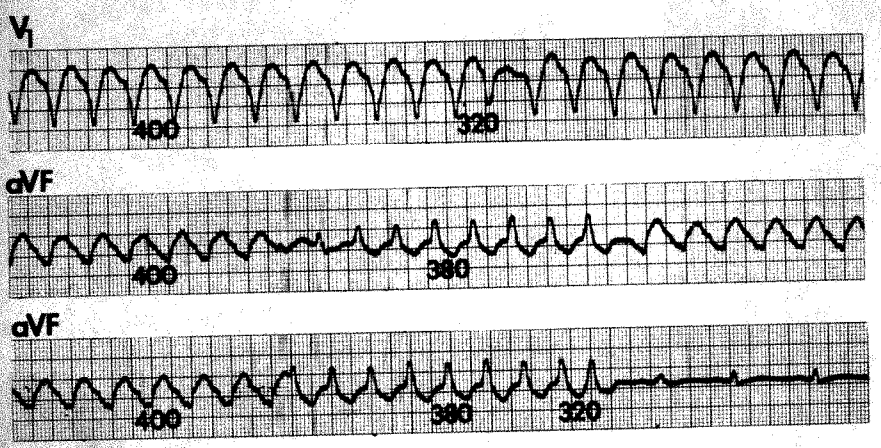

FIGURE 1. Termination of VT by the combination method in Patient 4. VT at a cycle length of 400 ms is present in all 3 rhythm strips. In the **top panel,** a single ventricular extrastimulus at a coupling interval of 320 ms fails to terminate the tachycardia. In the **middle panel,** bursts of ventricular pacing at a cycle length of 380 ms fail to interrupt the tachycardia. In the **bottom panel,** pacing at 380 ms and the addition of a single premature stimulus at a coupling interval of 320 ms abruptly terminate the tachycardia.

Two or 3 electrocardiographic leads I, II or aVF, and V_6 were simultaneously recorded with intracardiac electrograms from the right ventricular apex. Other intracardiac electrograms, including those from the left ventricle (6 patients), were also recorded in many but not all patients.

All data were displayed on a physiologic recorder (Electronics for Medicine VR16) and recorded on an ink jet system (Elema Mingograf) at paper speeds of 100 to 250 mm/s. Data were stored on magnetic tape (Honeywell 5600C) for subsequent retrieval.

Results

The overall results of using the combination method are summarized in Table II. This new method successfully terminated VT in 21 of the 25 study patients (84%), in each of whom rapid pacing and premature stimuli individually at similar cycle lengths and coupling intervals had failed to interrupt tachycardia. The paced cycle length and coupling interval of the premature stimulus (or stimuli) used in combination were, in all but 2 patients (Cases 3 and 8), the same paced cycle length and coupling interval(s) which proved ineffective in terminating VT when delivered individually. In these 2 patients, the ability to attain the same coupling interval used during the combination method was limited by ventricular refractoriness during tachycardia. Thus, during tachycardia the refractory period determined by a single extrastimulus during VT was longer than that achieved during the combination method. Of note is the fact that in both patients the introduction of 2 extrastimuli during tachycardia failed to terminate it despite

TABLE II Modes of Stimulation Used for Termination of Ventricular Tachycardia

Patient	VT CL (ms)	Individual Methods Attempted	Outcome	Paced CL Causing Acceleration	Paced CL in Combination Method
1	230	1, RVP	No change	. . .	220
2	330	1, RVP	No change	. . .	300
3	350	1, 2, RVP	No change	. . .	280
4	400	1, RVP	No change	. . .	380
5	300	1, RVP	No change	. . .	275
6	420	1, 2, RVP	No change	. . .	380
7	280	1, 2, RVP	No change	. . .	250
8	300	1, RVP	No change	. . .	260
9	440	1, 2, RVP	VT accelerated	275	350
10	370	1, 2, 3, RVP	VT accelerated	280	325
11	300	1, RVP	VT accelerated	225	250
12	500	1, RVP	VT accelerated	280	400
13	300	1, RVP	VT accelerated	225	280
14	350	1, 2, RVP	VT accelerated	250	300
15	320	1, RVP	VT accelerated	250	300
16	340	1, RVP	VT accelerated	250	320
17	240	1, RVP	No change	. . .	230
18	440	1, RVP	No change	. . .	350
19	320	1, RVP	No change	. . .	280
20	280	1, 2, RVP	No change	. . .	260
21	340	1, RVP	No change	. . .	300
22	260	1, 2, RVP	No change	. . .	230
23	450	1, RVP	No change	. . .	300
24	320	1, RVP	No change	. . .	300
25	450	1, 2, RVP	No change	. . .	350

CL = cycle length; Methods 1, 2, 3 = number of extrastimuli; RVP = rapid ventricular pacing.

the fact that the shortest coupling interval of the second extrastimulus was less than that used in the successful combination method. No patient in the study group manifested acceleration of tachycardia with the combination method.

None of the first group of 8 patients were taking antiarrhythmic drugs at the time of the study. In 6 of these 8 patients, the induced VT was terminated with the combination method when premature stimuli alone and overdrive pacing alone at comparable cycle lengths were unsuccessful (Fig. 1). Two patients (Cases 3 and 5) were unresponsive to this method as well—1 required cardioversion and in the other VT was terminated by an additional burst of rapid pacing at an extremely short cycle length (180 ms).

In 8 patients (Cases 9 to 16), premature stimuli delivered during VT failed to terminate the arrhythmia, and overdrive pacing at cycle lengths of 225 to 280 ms resulted in acceleration of VT in each case. The combination method was successful in terminating VT in 6 of these 8 patients. An example is shown in Figure 2. Overdrive pacing at a cycle length of 300 ms was ineffective, and pacing at a cycle length of 250 ms resulted in acceleration of VT; this was accompanied by loss of consciousness and cardioversion was required for termination. The same VT, however, could be reproducibly terminated by the combination method using overdrive pacing at a cycle length of 300 ms plus a single premature stimulus. Two patients (Cases 15 and 16) in this subgroup did not respond to the combination method and required cardioversion or a more rapid burst of pacing (cycle length 220 ms) than that previously causing acceleration.

In 9 patients (Cases 17 to 25) VT was successfully terminated with 1 or 2 premature stimuli or overdrive pacing before administration of antiarrhythmic drugs.

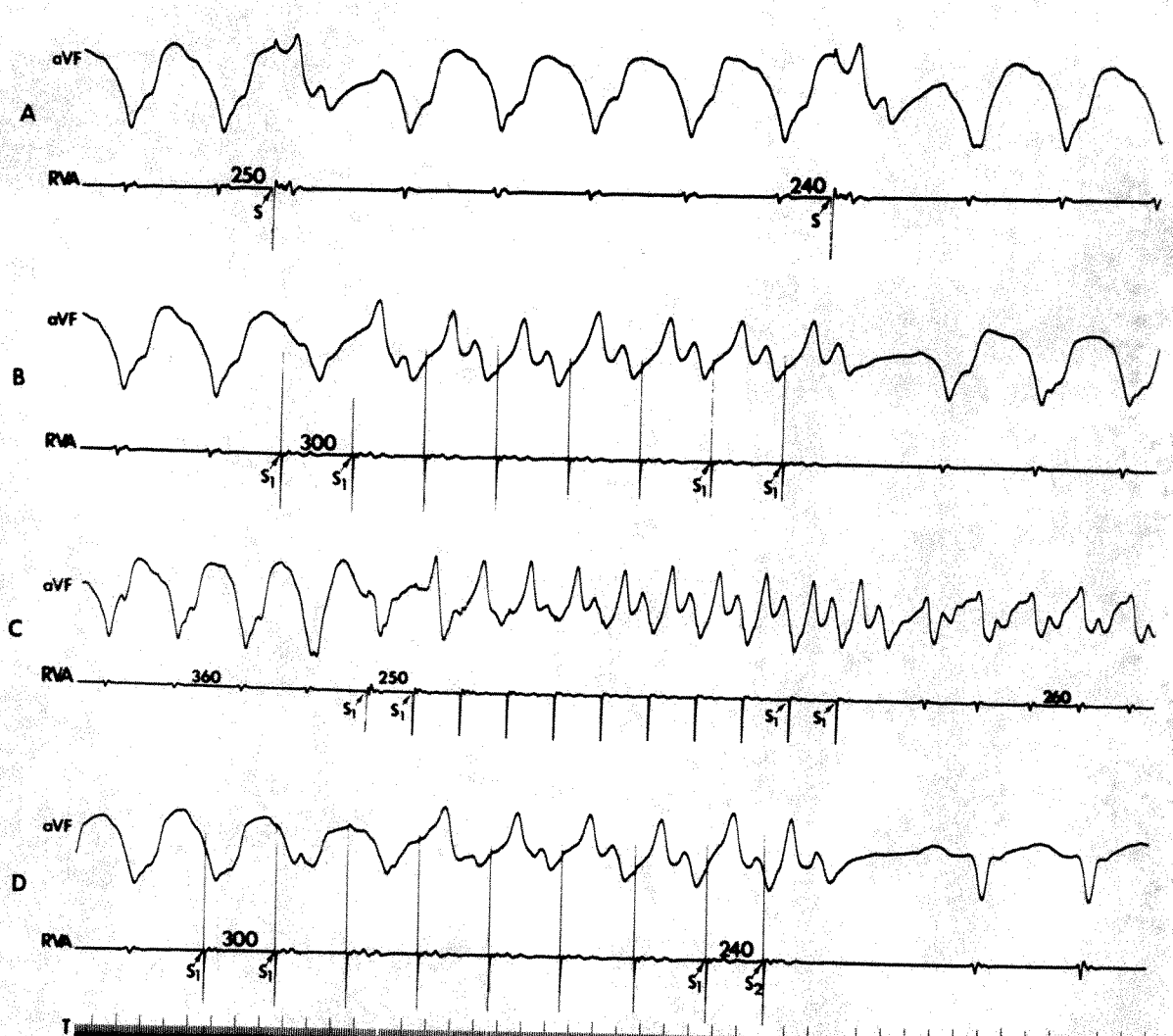

FIGURE 2. Combination method in Patient 14. Each panel shows recordings of lead aVF and the right ventricular apex (RVA). In **panel A,** a single premature stimulus (S) fails to terminate VT. In **panel B,** overdrive ventricular pacing at a paced cycle length of 300 ms (S_1—S_1) is also unsuccessful. In **panel C,** overdrive ventricular pacing at a paced cycle length of 250 ms results in acceleration of VT from a cycle length of 360 ms to 260 ms. A subsequent episode of VT is shown in **panel D.** In this case, a combination of overdrive pacing at a paced cycle length of 300 ms plus a single premature stimulus succeeds in restoring sinus rhythm. T = time line.

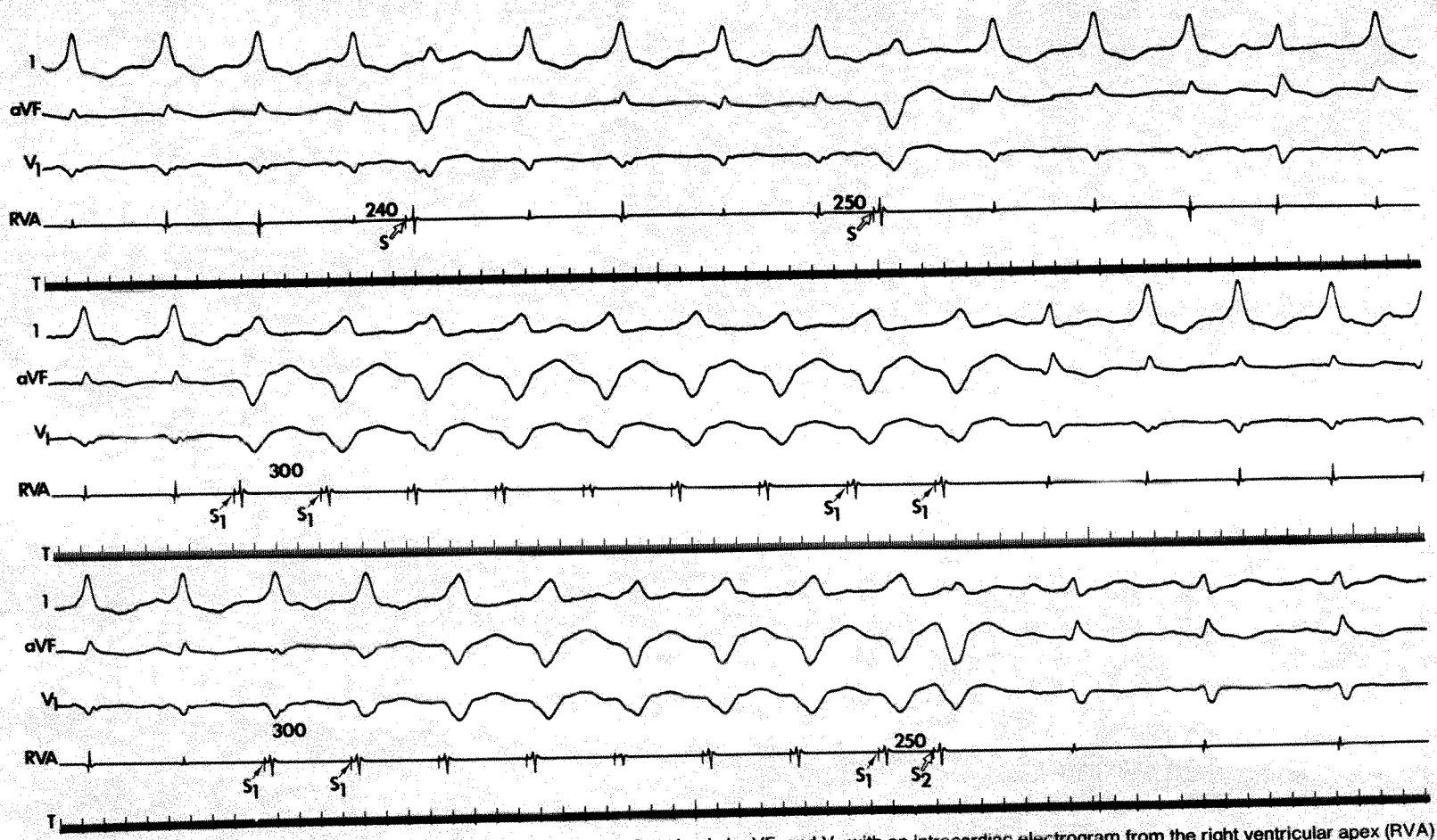

FIGURE 3. Example of combination method protocol. Each panel has surface leads I, aVF, and V_1 with an intracardiac electrogram from the right ventricular apex (RVA) and time lines (T). A left bundle branch block morphology VT is present. In the **top panel,** single premature stimuli (S) are introduced at the RVA at coupling intervals of 240 and 250 ms. Note that capture of the ventricles is accomplished with a change in the QRS morphology, but VT continues. Also evident in this panel is a sinus capture beat. In the **middle panel,** the VT is captured by overdrive ventricular pacing (S_1—S_1) at a paced cycle length of 300 ms, but the VT continues when the pacing is stopped. In the **bottom panel,** overdrive pacing at the same paced cycle length (300 ms) is followed by a premature stimulus (S_2) at a coupling interval previously shown ineffective. With this combination, however, sinus rhythm is restored.

However, after the administration of an antiarrhythmic agent (which failed to prevent induction of VT) these methods were no longer successful, despite slowing of the tachycardia. Thus, these patients represented a group in whom antiarrhythmic agents made termination of tachycardia more difficult. Tachycardia became incessant in 4 patients and 4 others exhibited sinus captures suggesting protection of the circuit. In all 9 patients, the combination method successfully terminated the induced VT. An example is shown in Figure 3. This patient had a left bundle branch block morphology VT with a cycle length of 400 ms. A sinus capture beat is present in the top panel A, indicating capture of a large part of the ventricular myocardium without interruption of VT. Single premature stimulus (top panel) and overdrive ventricular pacing (middle panel) could not terminate the VT. A combination of a single premature beat, plus overdrive pacing at the same coupling interval and paced cycle length previously shown to be ineffective, resulted in conversion of VT to sinus rhythm (bottom panel).

Discussion

The ability to initiate and terminate VT using programmed stimulation has been extremely useful in helping establish therapeutic regimens for patients with this arrhythmia.[1–10] The ability to reproducibly terminate tachycardia allows multiple studies to proceed without the need for multiple cardioversions. In addition, the efficacy of pacemaker therapy can be tested by assessing the modes of stimulation required for termination.

One of the major concerns, however, is that VT can be accelerated by pacing techniques, resulting in a more rapid tachycardia with hemodynamic embarrassment, degeneration to ventricular fibrillation, or both. Acceleration of VT by pacing has been reported to occur in 7 to 50% of episodes of VT and in up to 50% of patients with this arrhythmia.[3,4,9,10] Acceleration is most likely to occur with very vigorous pacing techniques such as multiple extrastimuli or bursts of rapid pacing.[3,4,9] As reported by Fisher et al[3] and Mason and Winkle,[4] as well as in our own experience, acceleration is most likely to occur when bursts of pacing are delivered at cycle lengths <250 ms to convert tachycardias which are rapid, with cycle lengths <300 ms. The incidence of acceleration with single or double extrastimuli is less.[3,4] Unfortunately, however, rapid tachycardias (that is, with a cycle length <300 ms) frequently require rapid bursts of pacing for termination.

Several factors determine the ability to terminate reentrant arrhythmias: the relation between the site of stimulation and site of the tachycardia circuit, the cycle length of the tachycardia, and the electrophysiologic characteristics (such as refractoriness and conduction) of local and intervening tissues. These factors determine when the tachycardia can be terminated by precisely timed stimuli.

As the ventricles are depolarized from the site of the VT circuit, the activation wave front spreads outward from this circuit to reach the site of stimulation. This activation wave front takes a finite period of time to reach the site of stimulation. It is followed by a wave of refractoriness that limits the prematurity with which a stimulus can be delivered at the site of stimulation. If the tachycardia cycle length is short or conduction of the stimulation impulse is slow, or both, a propagated stimulus often meets the oncoming wave front of activation, colliding with it and therefore failing to reach and penetrate the tachycardia circuit. Thus, the VT circuit is relatively protected by its own activation wave front and subsequent time of refractoriness. Overdrive pacing or the introduction of multiple extrastimuli reverses the activation wave front over the several delivered stimuli until the wave front of activation is reversed from the point of stimulation toward the tachycardia circuit. Even if the wave front of refractoriness is reversed by rapid pacing, the tachycardia may only be reset or, on occasion, may be stopped and then inadvertently started again.

While more rapid bursts of pacing may, in fact, terminate such tachycardias, under these circumstances, acceleration of the arrhythmia is also more likely.[3,4,10] The combination method of stimulation described herein represents an alternative to more rapid bursts of pacing. The ability to reverse refractoriness by rapid pacing allows a premature stimulus to be introduced earlier, so as to arrive at a critical time to produce bidirectional block within the tachycardia circuit and terminate the arrhythmia (Fig. 4). This method uses pacing at cycle lengths only slightly shorter than the tachycardia, which are less likely to induce acceleration. The overdrive pacing shortens local refractoriness, changes the wave front of activation and pattern of subsequent refractoriness, and allows a premature depolarization to reach the reentrant circuit at a critically timed interval to collide with the circulating impulse, thereby terminating the tachycardia. This system avoids the use of very rapid bursts of pacing which are likely to accelerate the tachycardia. The present study did not permit evaluation of whether shortening local refractoriness or changing the direction of the wave front of activation is the more important factor in the ability to terminate arrhythmias using this method. However, in only 2 patients could shortening of local refractory periods be implicated as related to the success of the new method.

Therapeutic uses: Acceleration of VT has been a problem with standard burst pacing or the use of multiple extrastimuli to terminate tachycardia during either a chronic drug study or an attempt to evaluate the most effective pacing method. Most patients who have a permanent pacemaker and are considered for the termination of recurrent tachycardia are taking such antiarrhythmic agents. The use of this newly described stimulation method assumes great importance in long-term drug studies since pharmacologic agents, particularly the membrane active types, are associated with slowing of the tachycardia.[2,8,9] Sinus captures suggesting protection of the circuit are also encountered

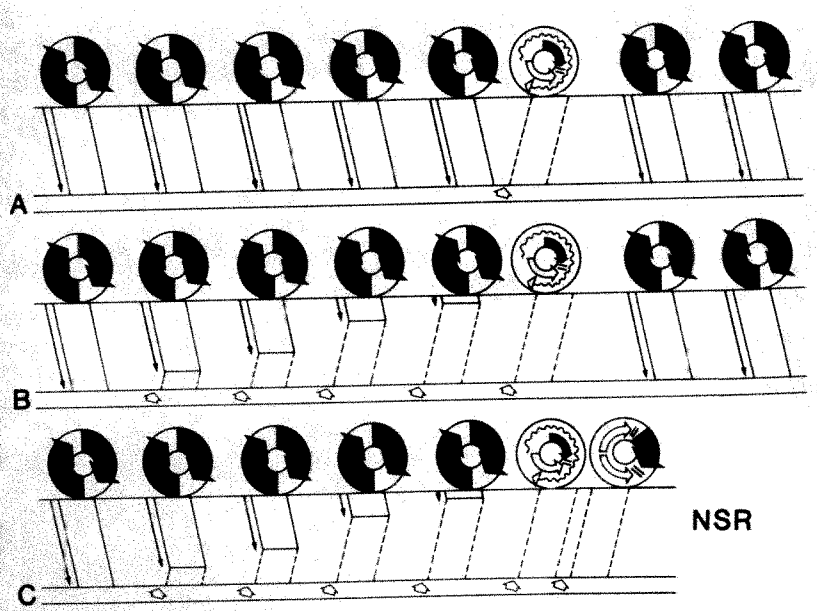

FIGURE 4. Mechanism of combination method. In each panel the assumed reentrant circuit is schematically shown as the circle. The **long, thin arrow** and **adjacent enclosed area** represent the activation wave front and obligatory accompanying refractory period. In **panel A,** a very early ventricular extrastimulus reaches the circuit but can only produce block in one direction, and therefore resets the circuit. In **panel B,** rapid pacing is shown to reverse the wave front of activation and refractoriness but still is only able to reset the tachycardia. In **panel C,** with the combination method, the premature stimulus reaches the circuit early enough to produce bidirectional block and terminate tachycardia. While the extrastimulus was delivered at the same coupling interval as in **panel A,** it reaches the tachycardia circuit earlier by the amount of time it took for the impulse to travel from the tachycardia circuit to the site of stimulation.

more frequently under these circumstances. In our experience, type I agents can make termination of VT more difficult or cause the tachycardia to become incessant, or both, in almost 25% of cases (unpublished observations). Although we cannot predict which patients will have this reaction; however, one obvious clue to such a circumstance is the presence of sinus captures (Fig. 3). These patients may be at relatively high risk for acceleration or degeneration to ventricular fibrillation when rapid pacing or multiple extrastimuli are introduced, due to the markedly prolonged conduction and refractoriness of intervening tissue produced by these drugs. These changes can lead to the development of local areas of block and chaotic conduction patterns between the site of stimulation and the reentrant circuit—circumstances which increase the tendency to fibrillation. Thus, the combination method of stimulation should be considered in patients who require type I drugs.

The development of more sophisticated pacemakers for the management of VT should probably incorporate the ability to introduce premature stimuli after a given number of drive stimuli during tachycardia. The laboratory demonstration of the efficacy of this type of pacemaker is important when pacing therapy is a consideration in the management of these arrhythmias.

Limitations: The present study did not address several aspects of the pacing protocol that might have bearing on the efficacy and safety of the new method of termination. These include the coupling interval of the first beat of the train of stimuli to the tachycardia, the rate of overdrive pacing, the duration of overdrive pacing, and the coupling interval of premature stimuli.

The coupling interval of the onset of the train of stimuli was variable in the present study, since the burst was delivered in an asynchronous mode. For example, a train of stimuli at a cycle length of 300 ms could have begun with the first stimulus of that train having a variable coupling interval to the tachycardia of 200 to 300 ms. The variable coupling interval may be important with regard to the ability to terminate or accelerate tachycardia.

The rate of duration of rapid pacing were not studied either. The combination method of stimulation might have been more effective if pacing had been continued for a longer period to ensure complete reversal of the activation wave front to the tachycardia, in order to more rapidly facilitate penetration of the tachycardia. On the other hand, more rapid pacing rates will probably reverse the activation wave front more quickly; thus, a shorter burst would be necessary. However, it is known that the slower the overdrive, that is, with overdrive <120% of the VT cycle length, the lower the incidence of acceleration.[10] This slower rate may require a longer duration of pacing and hence a greater number of captures to ensure a total change in the direction of the wave front and recovery of excitability, which allows the ventricular premature depolarization to reach and penetrate the circuit to terminate tachycardia. More rapid rates, which may be more prone to accelerate tachycardia, require a shorter duration of pacing in order to capture the ventricles and change the wave front of activation. The exact paced rate and duration, as well as coupling intervals, which are both safest (with respect to acceleration) and most efficient should be determined for each patient.

Conclusion: Thus, while this combination method of termination of tachycardia appears to be a promising new mode of stimulation which can terminate tachycardia safely and efficiently, further studies are needed to ascertain the role of varying the coupling interval of the first stimulus of the train of stimuli, as well as the rate and duration of the train, and the coupling intervals of the premature stimuli. This will require the use of sophisticated stimulators, and indicates the complex requirements of antitachycardia pacing systems which need to be developed in the future.

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Termination of Ventricular Tachycardia: Role of Tachycardia Cycle Length

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The mode of termination of ventricular tachycardia (VT) and its relation to tachycardia cycle length was evaluated in 139 patients. Tachycardia was terminated by programmed stimulation in 110 patients (79%) and cardioversion was required in 29 patients (21%). Single, double, and triple ventricular extrastimuli terminated the tachycardia in 23 of 85 (27%), 39 of 62 (63%), and 7 of 16 patients (44%), respectively. In all patients requiring 1 extrastimulus, in 35 patients (90%) requiring 2 extrastimuli, and in 6 patients (86%) requiring 3 extrastimuli, the tachycardia cycle length exceeded 300 ms. Rapid ventricular pacing terminated tachycardia in 41 of 54 patients (76%). In 21 (51%) of these patients the tachycardia cycle length exceeded 300 ms. However, rapid ventricular pacing caused acceleration of the arrhythmia in 19 patients (35%). The ability of procainamide to modify the termination of VT was studied in 23 patients. In 7 of these patients (30%) procainamide increased the tachycardia cycle length by 49 ± 42 ms ($p < 0.01$) and did not modify the mode of termination. In 6 patients (26%) procainamide increased cycle length by 142 ± 108 ms ($p < 0.01$), but termination was more difficult. In 10 patients (44%) procainamide increased the cycle length by 138 ± 110 ms ($p < 0.001$) and termination was easier. We conclude that termination of VT by timed extrastimuli requires a tachycardia cycle length longer than 300 ms. Rapid pacing or cardioversion is usually required when the cycle length is less than 300 ms. Although procainamide slows tachycardia, it can unpredictably make termination more difficult in 1 of 4 patients.

Programmed ventricular stimulation is increasingly used to evaluate the mechanisms and therapy of recurrent VT. Previous studies have shown that in the majority of patients in whom VT can be initiated by programmed ventricular stimulation, the arrhythmia can also be terminated by appropriately timed extrastimuli or by rapid ventricular pacing.[1–5] The pacing techniques employed during electrophysiologic testing may serve as a guide for chronic pacemaker therapy of drug-resistant ventricular arrhythmias.[6] It has been suggested that the mode of termination of VT is related to tachycardia cycle length. However, the relation between the specific mode of termination and the tachycardia cycle length has never been systematically evaluated in a large group of patients. The aims of this study are (1) to analyze the relation of mode of termination of VT to tachycardia cycle length, and (2) to assess the influence of procainamide on tachycardia cycle length and mode of tachycardia termination.

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Methods

Patients: The study population consisted of 139 patients with recurrent VT or cardiac arrest in whom sustained VT was induced by programmed ventricular stimulation. There were 104 men and 35 women ranging in age from 8 to 74 years. Coronary artery disease was present in 101 patients, miscellaneous cardiac abnormalities (cardiomyopathy, repair of tetralogy of Fallot, hypertensive cardiovascular disease, and mitral valve prolapse) in 22, and no documented clinical organic heart disease in the remaining 16.

Electrophysiologic procedures: After informed consent was obtained, the patients underwent electrophysiologic

testing in the nonsedated postabsorptive state. The administration of all antiarrhythmic agents was discontinued at least 48 hours before the procedure. Three or more electrode catheters were inserted percutaneously or by venous cutdown and positioned in the heart under fluoroscopic guidance. These usually included quadripolar catheters in the right atrium and right ventricle and a tripolar catheter at the atrioventricular junction for recording His bundle electrograms. Electrical stimulation was performed with a specially designed digital stimulator and isolated constant current source (Bloom Associates, Narberth, Pennsylvania). The stimuli were rectangular pulses 1 ms in duration at twice diastolic threshold. Intracardiac recordings were filtered at 30 to 500 Hz and simultaneously recorded with 3 electrocardiographic leads. Stimulation techniques for initiating VT included the introduction of single, double, triple, or quadruple ventricular extrastimuli from the right ventricle during sinus rhythm or during ventricular pacing at 2 or 3 different basic cycle lengths. The stimulation protocol during VT included the introduction of 1 ventricular extrastimulus from the right ventricle scanning diastole until ventricular refractoriness was reached. If a single stimulus did not terminate tachycardia, 2 and sometimes 3 extrastimuli were introduced; the coupling intervals of the extrastimuli were varied until refractoriness was reached. If timed extrastimuli failed to terminate the tachycardia or if hemodynamic embarassment was marked, bursts of rapid ventricular pacing for 5 to 60 seconds starting at a cycle length 10 ms shorter than the tachycardia cycle length were employed. The protocol was altered to begin with more vigorous pacing techniques if tachycardia was hemodynamically unstable.

The effect of procainamide on tachycardia cycle length and termination was evaluated in 23 patients in whom tachycardia could be induced after the intravenous administration of procainamide 500 to 2,000 mg at 50 mg/min.

Results

Termination of VT: The ability of programmed ventricular stimulation to terminate VT could be studied in 123 patients. In 16 patients, programmed ventricular stimulation could not be evaluated because the tachycardia caused hemodynamic deterioration and immediate cardioversion was required. VT could be terminated by some form of programmed stimulation in 110 patients (79%). In 13 patients rapid ventricular pacing caused acceleration of the tachycardia and cardioversion was ultimately employed to terminate the arrhythmia.

Effect of programmed ventricular stimulation during VT (Table I): A single ventricular premature stimulus terminated VT in 23 of the 85 patients (27%) in whom this technique was tested. Double and triple ventricular extrastimuli terminated the tachycardia in 39 of 62 patients (63%) and 7 of 16 patients (44%), respectively. Rapid ventricular pacing terminated the tachycardia in 41 of the 54 patients (76%) in whom it was attempted.

Acceleration of VT (shortening of the tachycardia cycle length by 30 ms or more) occurred in 24 (20%) of the 123 patients who underwent ventricular stimulation during VT. Single, double, and triple extrastimuli caused acceleration of VT in a total of 5 patients, none of whom needed cardioversion. Rapid ventricular pacing produced acceleration in 19 of 54 patients (35%), 13 of whom required cardioversion because of hemodynamic deterioration or degeneration to ventricular fibrillation. The mean tachycardia cycle length was 325 ms (range 315 to 330) in the 5 patients in whom single (1 patient), double (2 patients), and triple extrastimuli (2 patients) produced acceleration of the tachycardia. The mean tachycardia cycle length was 282 ms (range 240 to 400) in the 19 patients whose tachycardia was accelerated by rapid ventricular pacing.

TABLE I Effects of Programmed Ventricular Stimulation (PVS) During VT (123 Patients)

Mode of PVS	Patients (n)	Termination		Acceleration	
		n	%	n	%
1 VES	85	23	27	1	1.2
2 VES	62	39	63	2	3.2
3 VES	16	7	44	2	13
RVP	54	41	76	19	35

RVP = rapid ventricular pacing; VES = ventricular extrastimuli.

Relation between mode of termination of VT and tachycardia cycle length (Table II): The tachycardia cycle length was longer than 300 ms in all 23 patients in whom a single ventricular extrastimulus terminated the arrhythmia, and in 16 of these patients the cycle length was longer than 400 ms. The tachycardia cycle length exceeded 300 ms in 35 of the 39 patients (90%) in whom tachycardia was terminated by 2 ventricular extrastimuli and in 6 of 7 patients (86%) in whom 3 ventricular extrastimuli terminated tachycardia. In 45 of the 50 patients who had a tachycardia cycle length <300 ms, rapid ventricular pacing (20 patients) or cardioversion (25 patients) was required to terminate tachycardia.

Effect of procainamide on mode of termination of VT (Table III): The effect of procainamide on the ability to terminate VT was studied in 23 patients in whom the drug failed to prevent initiation of VT. The mean tachycardia cycle length was 280 ms (range 180 to 390) before administration of procainamide and was 392 ms (range 200 to 670) after procainamide with a mean increase of 112 ± 99 ms (range 0 to 370) ($p < 0.00001$). The average dose of procainamide was 1,595 mg (500 to 2,000), resulting in a mean plasma level of 11.4 μg/ml (range 4.3 to 27.2). In 7 patients (30%) the mode of termination before and after procainamide was

TABLE II Relation of Mode of Termination of VT With Cycle Length (139 Patients)

Mode of Termination	VT Cycle Length (ms)				
	400–500	350–400	300–350	<300	VT (n)
1 VES	16	5	2	...	23
2 VES	12	15	8	4	39
3 VES	...	3	3	1	7
RVP	1	5	15	20	41
Cardioversion	...	2	2	25	29
VT (n)	29	30	30	50	139

Abbreviations as in Table I.

TABLE III Effect of Procainamide on Mode of Termination of VT (23 Patients)

Effect	Patients n	Patients %	Mean Dose (mg)	Mean Plasma Level (μg/ml)	Mean VT Cycle Increase (ms)
Unchanged	7	30	1,460	7.5	49 ± 42 (p <0.01)
Harder	6	26	1,500	12.9	142 ± 108 (p <0.01)
Easier	10	44	1,750	13.7	138 ± 110 (p <0.001)

similar. The mean increase in the tachycardia cycle length in these patients was 49 ± 42 ms (p <0.01). In 6 patients (26%) in whom procainamide produced a mean increase of 142 ± 108 ms (p <0.01) in the tachycardia cycle length, termination was more difficult. In 2 of these patients a single premature stimulus terminated the tachycardia before procainamide, but 2 extrastimuli were required after procainamide (Fig. 1). In 3 patients rapid ventricular pacing terminated the arrhythmia before procainamide but was no longer successful after procainamide. All 3 patients required cardioversion to sinus rhythm. In the remaining patient the cycle length increased from 275 to 600 ms after procainamide, but the arrhythmia became incessant and could not be terminated by pacing techniques or cardioversion. In 10 patients (44%) in whom procainamide increased the cycle length by 138 ± 110 ms (p <0.001) tachycardia termination was facilitated. Tachycardia terminated spontaneously in 4 of these patients. In 4 others tachycardia was terminated by rapid pacing at cycle lengths 40 to 175 ms longer than before procainamide. In 1 patient procainamide made it possible to terminate tachycardia with 2 extrastimuli instead of rapid pacing. In the last patient rapid pacing caused degeneration to ventricular fibrillation in the baseline state, whereas after procainamide rapid pacing at a longer cycle length than that during control terminated tachycardia.

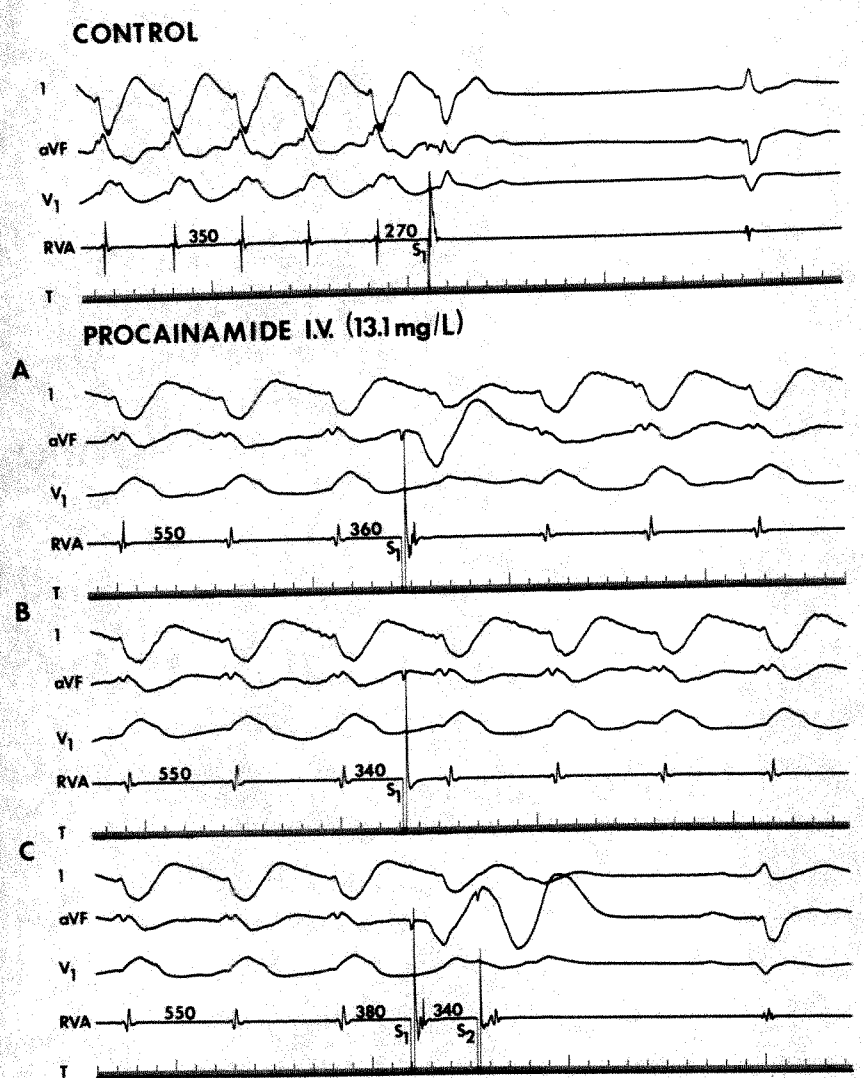

FIGURE 1. Control: VT with a cycle length of 350 ms is terminated by a single ventricular extrastimulus delivered at 270 ms before procainamide administration. Procainamide (13.1 mg/liter): **Panel A,** after procainamide administration the tachycardia cycle length has increased to 550 ms. A single ventricular extrastimulus introduced at 360 ms fails to terminate tachycardia. **Panel B,** prolongation of ventricular refractoriness by procainamide prevents a single ventricular extrastimulus delivered at 340 ms from capturing the ventricle. **Panel C,** 2 ventricular extrastimuli at 380 and 340 ms are required to terminate VT after procainamide. In each panel surface leads I, aVF, and V_1 are simultaneously recorded with a right ventricular apical electrogram (RVA). T = time lines.

Discussion

Comparison with previous studies: Our data corroborate previous studies[1–5] demonstrating that pacemaker termination of VT can be performed in approximately 80% of patients. However, the mode of stimulation required to terminate VT in this study differs from that of earlier reports. In 1976 Wellens et al[1] showed that a single ventricular extrastimulus terminated induced VT in 20 of 43 patients (47%) and 2 or 3 ventricular extrastimuli were required in 13 patients (30%). An earlier report from this institution showed that VT was terminated by a single ventricular extrastimulus in 9 of 17 patients (53%), and 2 ventricular extrastimuli or rapid ventricular pacing was required in 6 patients (35%).[4]

The present study demonstrates that of 123 patients who underwent programmed ventricular stimulation during tachycardia a single ventricular extrastimulus terminated the arrhythmia in only 23 patients (19%) and that more than 1 ventricular extrastimulus or rapid ventricular pacing was required in 87 patients (71%). These observations suggest that more aggressive pacing techniques are frequently required to terminate ventricular tachycardia.

The cause for this discrepancy may be related to a change in patient population. Many of our more recent patients presented with hemodynamic collapse due in large part to faster tachycardia rates. The study by Wellens et al[1] and our earlier study[4] were largely composed of patients with a tachycardia cycle length ≥300 ms. Neither of these studies nor previous studies carefully analyzed the effect of tachycardia cycle length on various modes of termination.

Furthermore, we observed that in our patient population with VT, more aggressive stimulation is required to induce VT. Often 3 and sometimes 4 extrastimuli are required to induce tachycardia. Hence, we may be dealing with a tachycardia that has a reentrant circuit that seems more difficult to penetrate. An additional investigation on the relation between mode of initiation and mode of termination seems necessary.

Relation between tachycardia cycle length and effect of programmed stimulation: Termination of VT by single, double, or triple ventricular extrastimuli usually required a tachycardia cycle length >300 ms. Timed extrastimuli produced acceleration of VT in only a small number of patients, none of whom needed cardioversion. Rapid ventricular pacing could terminate VT in 40% of patients with cycle lengths <300 ms. However, this technique caused acceleration of the stable tachycardia in 35% of patients, a finding similar to the 43% incidence reported by Fisher et al.[3] Furthermore, most of the patients (13 of 19) with this complication required cardioversion because of rapid hemodynamic deterioration. Although rapid ventricular pacing techniques can be useful and their complications can be rapidly corrected in the electrophysiologic laboratory, we believe that because acceleration or degeneration to ventricular fibrillation is not uncommon, this mode of stimulation should be rarely employed, if at all, for chronic pacemaker therapy of VT.

Effect of procainamide on termination of VT: Wellens et al[7] showed that drugs that can slow the tachycardia can also facilitate termination. This finding was true in 44% of our 23 patients in whom we could study the mode of termination before and after procainamide administration. However, this drug made termination more difficult in 26% of our patients. The plasma level of procainamide or tachycardia cycle length was not a useful predictor of the effects on termination. Several factors can influence the ability to terminate VT: tachycardia cycle length, site of stimulation in relation to the site of tachycardia circuit, and ventricular conduction and refractoriness.[1–4] Modifications of these factors by pharmacologic agents, stimulation at different sites, or increasing the current strength can influence the ability of an impulse to reach the reentrant circuit at a critical time to terminate the arrhythmia. Although modification of tachycardia cycle length by procainamide favors facilitation of termination, the increased ventricular refractoriness and prolonged intraventricular conduction produced by the drug can make termination more difficult (Fig. 1). The interplay of these factors will determine the effect of procainamide on tachycardia termination. Previous investigators have shown variable effects on reentrant tachycardia and ventricular tissue with procainamide.[7,8] Our demonstration of poor correlation between cycle length slowing by procainamide and termination of VT supports these earlier observations and suggests that the effect of procainamide on intraventricular conduction and refractoriness may be a more important factor. Therefore, increasing the tachycardia cycle length with drugs does not necessarily assure that pacemaker termination will be facilitated. Thus, the potential value of pacemaker and drug combination requires individual evaluation.

Limitations: Although our patient population is the largest heretofore reported, it probably represents a selected subgroup of patients with more refractory ventricular arrhythmia. Extrapolation of our findings to other patient populations may not be appropriate. In addition, because of the retrospective format of this study, there are methodologic limitations such as nonuniformity of stimulation protocol. Moreover, all methods of stimulation were not studied in each patient because of the speed with which termination was required clinically and the various staff members performing the studies. Another limitation of the present study is the use of the right ventricle usually apex or low septum as the stimulating site in this study. Changing the pacing site to the right ventricular outflow tract or the left ventricle might have produced different results, particularly after procainamide. However, because most permanent pacemakers are implanted at the right ventricular apex, our observations may still have clinical relevance. Another limitation is that stimulation was performed at twice the diastolic threshold which was

always less than 2 mA. Most permanent pacemakers deliver between 5 and 10 mA, so that our study may underestimate the ability of less aggressive stimulation to terminate the tachycardia. A recent observation from our laboratory has demonstrated that termination of VT by 1 or 2 ventricular extrastimuli can be facilitated by increasing the current strength to 5 to 10 mA.[9]

Conclusions: We believe that the following conclusions can be helpful to the clinician in performing electrophysiologic testing of patients with VT and in selecting a proper mode of termination when right ventricular stimulation is employed: (1) In approximately 80% of patients in whom VT can be induced the arrhythmia can be terminated by programmed ventricular stimulation. (2) Termination by timed extrastimuli usually requires a tachycardia cycle length >300 ms. (3) In patients with tachycardia cycle length <300 ms, rapid ventricular pacing or cardioversion is usually required to terminate the arrhythmia. (4) When performing rapid ventricular pacing, the clinician should be alert to the possible acceleration of tachycardia which can occur in over one third of patients. Therefore, we do not recommend that this mode of stimulation be employed for chronic pacemaker therapy of VT. (5) Although procainamide can slow the tachycardia and facilitate termination, it can make termination more difficult in 1 of 4 patients. This potential problem should be tested before treating a patient with a combination of drug therapy plus a pacemaker.

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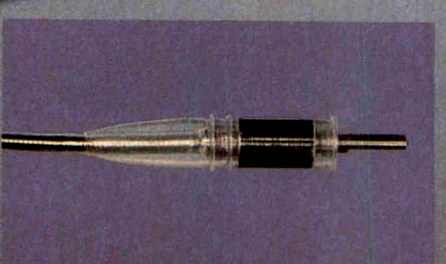

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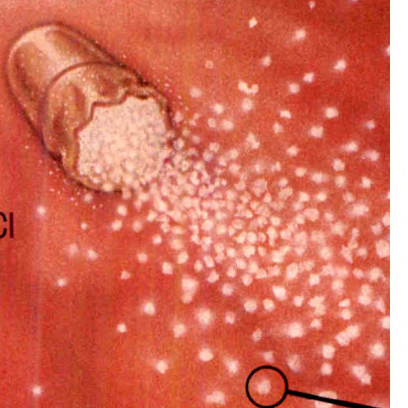

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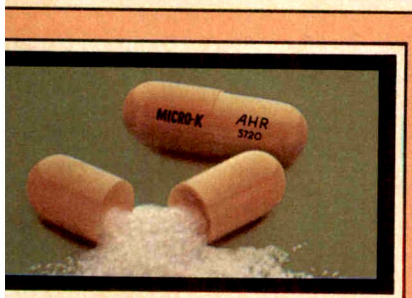

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Potassium depletion may occur whenever the rate of potassium loss through renal excretion and/or loss from the gastrointestinal tract exceeds the rate of potassium intake. Such depletion usually develops slowly as a consequence of prolonged therapy with oral diuretics, primary or secondary hyperaldosteronism, diabetic ketoacidosis, severe diarrhea, or inadequate replacement of potassium in patients on prolonged parenteral nutrition. Potassium depletion due to these causes is usually accompanied by a concomitant deficiency of chloride and is manifested by hypokalemia and metabolic alkalosis. Potassium depletion may produce weakness, fatigue, disturbances of cardiac rhythm (primarily ectopic beats), prominent U-waves in the electrocardiogram, and in advanced cases, flaccid paralysis and/or impaired ability to concentrate urine.

Potassium depletion associated with metabolic alkalosis is managed by correcting the fundamental causes of the deficiency whenever possible and administering supplemental potassium chloride, in the form of high potassium food or potassium chloride solution, capsules or tablets. In rare circumstances (e.g., patients with renal tubular acidosis) potassium depletion may be associated with metabolic acidosis and hyperchloremia. In such patients potassium replacement should be accomplished with potassium salts other than the chloride, such as potassium bicarbonate, potassium citrate, or potassium acetate.

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3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases, supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: *Hyperkalemia.* In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.

The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustments.

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Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and may be minimized by taking the dose with meals or by reducing the dose.

Intestinal bleeding, ulceration, perforation and obstruction have been reported in patients treated with solid dosage forms of potassium salts and may occur with Micro-K Extencaps (see Contraindications and Warnings).

One of the most severe adverse effects of potassium supplementation is hyperkalemia (see Contraindications, Warnings, and Overdosage).

Skin rash has been reported rarely with potassium preparations.

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiogram changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following: (1) elimination of foods and medications containing potassium and of potassium-sparing diuretics; (2) intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml; (3) correction of acidosis, if present, with intravenous sodium bicarbonate; (4) use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

Dosage and Administration: The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient, but typically is in the range of 2 to 3 Micro-K Extencaps per day (16 to 24 mEq K) for the prevention of hypokalemia and 5 to 12 Micro-K Extencaps (40 to 96 mEq K) or more per day for the treatment of potassium depletion. If more than 2 Micro-K Extencaps are prescribed per day, the total daily dosage should be divided into two or more separate doses.

How Supplied: Pale orange capsules (Extencaps), each containing 600 mg microencapsulated potassium chloride (equivalent to 8 mEq K) in bottles of 100 (NDC 0031-5720-63), and 500 (NDC 0031-5720-70) and Dis-Co® unit dose packs of 100 (NDC 0031-5720-64).

Animal Toxicology: The ulcerogenic potential of microencapsulated KCl was studied in anesthetized cats by direct applications on exteriorized gastric mucosa. The microcapsules of KCl were found to be non-ulcerogenic and significantly less irritating than wax-matrix tablets and 20% solution of KCl.

In groups of monkeys (up to 8 monkeys per group) receiving different formulations of potassium chloride at equivalent daily dosage (2400 mg KCl) for four and one-half days, Micro-K Extencaps showed no tendency to cause intestinal ulceration (similar to liquid KCl and a wax-matrix preparation but in contrast to an enteric-coated KCl tablet) and minimal gastric irritation (less than a wax-matrix preparation).

July 1980

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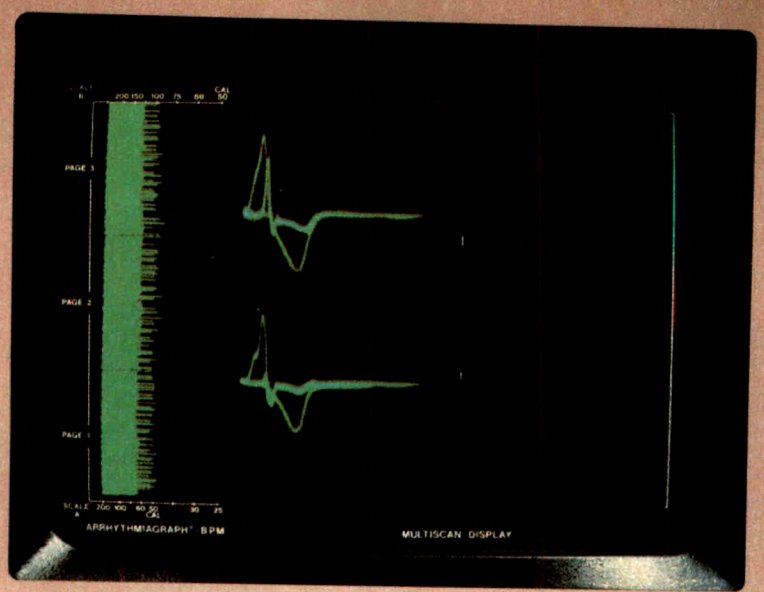

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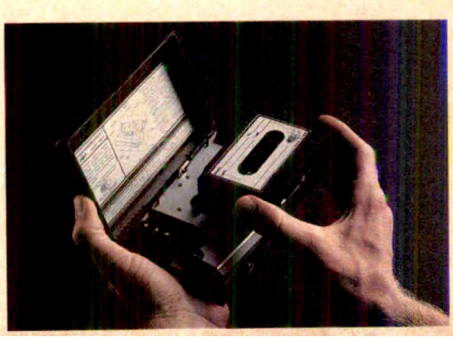

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Two-Dimensional Echocardiographic Assessment Of Dextrocardia: A Segmental Approach

JAMES C. HUHTA, MD, DONALD J. HAGLER, MD, JAMES B. SEWARD, MD, ABDUL J. TAJIK, MD, PAUL R. JULSRUD, MD, and DONALD G. RITTER, MD

Two-dimensional echocardiography was used in the prospective evaluation of 40 patients with the clinical diagnosis of dextrocardia. A segmental analysis of the situs, connections, ventricular anatomy, and chamber positions was utilized for a complete diagnostic assessment. An adequate examination was possible in 33 of these patients; the findings were confirmed by cardiac catheterization and angiography in 31 patients and at operation in 26.

Use of the location of the liver and the drainage of the hepatic veins and inferior vena cava allowed atrial visceral situs to be defined in 33 patients (solitus 21, inversus 9, and ambiguous 3). Pulmonary venous connections were correctly identified in 27. In 33 patients, atrioventricular (AV) and ventriculoarterial connections and ventricular anatomy were correctly predicted. Twenty patients had 2 separate well-developed ventricles. Ventriculoarterial connections were determined correctly in all 20 patients: concordant in 5, discordant in 6, double-outlet right ventricle in 5, and single-outlet right ventricle (pulmonary atresia) in 4. In 16 patients a ventricular septal defect was correctly identified. In the remainder the ventricular septum was intact.

Thirteen patients had univentricular heart: 8 had 2 AV valves (double-inlet ventricle), 3 had common AV inlet, and 2 had atresia of 1 AV connection.

Two-dimensional echocardiography allowed the accurate assessment of complex congenital heart defects associated with dextrocardia. Utilizing a segmental approach, one can correctly predict atrial-visceral situs, ventricular morphology and situs, and AV and ventriculoarterial connections.

Two-dimensional echocardiography has substantially expanded the horizons for accurate noninvasive diagnosis of congenital cardiac defects. A number of reports have demonstrated the utility of 2-dimensional echocardiography in diagnosing complex forms of congenital heart disease, such as transposition of the great arteries, double-outlet right ventricle, univentricular heart, and AV discordance.[1–6] Analysis of complex congenital cardiac anatomy requires an organized and detailed approach. Cardiac pathologists have emphasized the importance of a logical sequential or segmental approach in the analysis of multiple complex congenital heart lesions involving abnormalities of chamber position and connections.[7–10] These methods have been expanded to allow the premortem diagnosis of such lesions, using cardiac catheterization and biplane angiographic techniques.[11] M-mode echocardiographic studies have attempted such correlation,[12,13] but it is only with the advent of 2-dimensional echocardiography that a noninvasive segmental analysis of cardiac anatomy has been feasible.

Dextrocardia is a condition in which the major axis of the heart (base to apex) points to the right, not as a consequence of acquired disease but as a result of congenital malposition.[7,11] Dextrocardia may exist with situs solitus, situs inversus, or situs ambiguous. Because a broad spectrum of cardiac anomalies may accompany dextrocardia, this group of anomalies appears to represent a critical test of the segmental approach for the 2-dimensional echocardiographic assessment of complex congenital heart disease. After our review of patients with AV discordance,[6] it was apparent that a segmental approach was necessary for the accurate and

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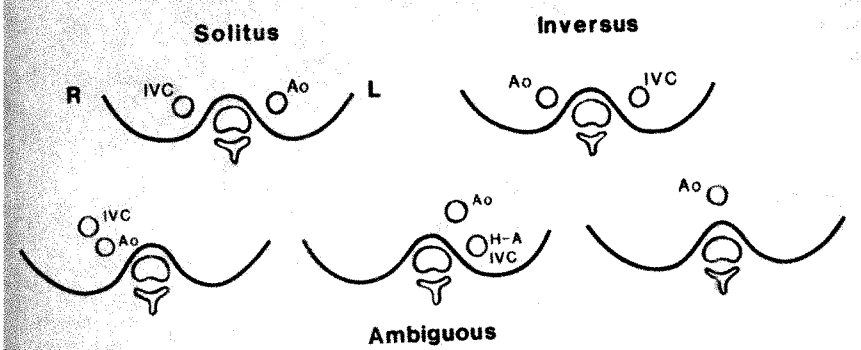


FIGURE 1. Drawing illustrating the respective orientations of the inferior vena cava and the abdominal aorta relative to the spine in situs solitus, situs inversus, and situs ambiguous. In situs ambiguous, the inferior vena cava (IVC) and aorta (Ao) tend to lie on the same side of the spine, or the inferior vena cava may not be visualized. A vascular structure posterior to the aorta may represent an azygous or hemizygous continuation (H-A) with interrupted inferior vena cava.

thorough diagnosis of complex congenital heart disease. We utilized the approach proposed with that study to analyze patients who had a clinical diagnosis of dextrocardia (Table I).

Methods

Between October 1977 and November 1981, 40 patients with the clinical diagnosis of dextrocardia were examined by 2-dimensional echocardiography. Seven patients were subsequently excluded because the examinations were not technically adequate to define the situs or the details of intracardiac anatomy. Of the remaining 33 patients, the results of cardiac catheterization and angiography were available in 31, and surgical confirmation of the cardiac anatomy was available in 26. In 2 patients with isolated dextrocardia, 2-dimensional echocardiography revealed normal cardiac anatomy, and no further evaluation or treatment was deemed necessary. The ages of the patients at the time of examination ranged from 2 days to 29 years, with a mean of 8.5 years. Thirteen patients previously had palliative surgery, including Glenn and Blalock-Taussig shunts. One patient had previous intracardiac surgery, with closure of a ventricular septal defect and mitral valve replacement.

TABLE I Segmental Approach for Prospective 2-Dimensional Echocardiographic Study of Complex Congenital Heart Disease

1. Atrial and visceral situs
   - Caval position and connection
   - Hepatic veins
   - Coronary sinus
   - Pulmonary venous connection
2. AV connections and AV valve morphology
   - Commitment (AV malalignment-overriding, criss-cross)
   - Insertion (chordal attachment-straddling)
   - Leaflet numbers
   - Papillary muscles (position, number, abnormality-parachute)
   - Leaflet abnormalities (cleft, thickening-stenosis)
3. Ventricular situs and morphology
   - Cardiac position (levocardia, dextrocardia, mesocardia)
   - Ventricular relations (anterior, posterior, superior, inferior, right, left)
   - AV valve attachment
   - Shape (ellipsoid, crescentic, triangular)
   - Trabecular pattern
   - Papillary muscles (2 discrete versus multiple irregular)
4. Great artery relations
   - Position (normal, side-by-side, dextro, levo)
   - Ventriculoarterial connection
   - Override
   - AV valve continuity (subvalvular conus)
   - Identification
     - Posterior course and bifurcation of pulmonary artery
     - Anterior and superior course of aorta

Reprinted, with permission, from Hagler et al.[6]

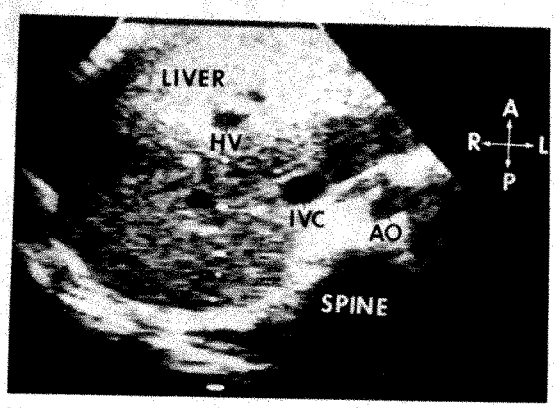
Two-dimensional echocardiographic examinations were performed using the Varian 3000, Varian 3400, or the American Technology Laboratory (Mark V) wide-angle sector echocardiograph. The examinations were carried out with the knowledge that the patients had dextrocardia, as determined by standard posteroanterior chest roentgenogram. The patients were examined using left parasternal long- and short-axis views, right parasternal long- and short-axis views, right apical and subcostal long-axis and 4-chamber views, and suprasternal long- and short-axis views. The right parasternal long- and short-axis scans were obtained utilizing right parasternal transducer positions similar to those used in left parasternal scans. The transducer orientation was maintained to achieve image orientation similar to that in the standardized left parasternal views, that is, superior and leftward structures observed on the right of the video image. Similarly, for apical and subcostal views, image orientation was maintained to keep leftward structures located on the right of the video image. We emphasize that if cardiac structures cannot be adequately seen from 1 position, alternate scans from multiple and atypical positions should be employed. Apical 4-chamber and subcostal 4-chamber long- and short-axis views must be included in the examination.

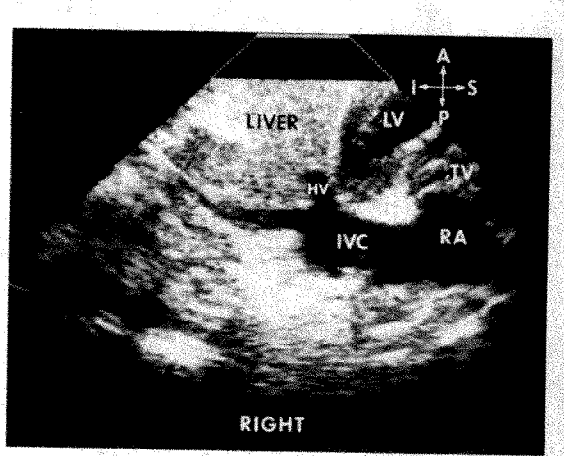
After our initial experience in examining such patients, left parasternal long- and short-axis views were found particularly helpful in some cases in delineating great artery relations. Subcostal and apical 4-chamber long-axis views are helpful in delineating ventricular morphology and AV and ventriculoarterial relations. Subcostal scans were frequently utilized because of the retrosternal position of cardiac structures. Transducers of 2.25, 3, and 3.5 MHz were employed, depending on the instrument used and the patient size. At the time of this review, without knowledge of the details of the previous examination, the recorded videotapes were independently examined and an assessment was made using the segmental method described. After this review, the results were compared with the original 2-dimensional echocardiographic reports, and a combined data base was obtained; this was then compared with the angiographic and surgical findings. Photographs (35 mm) were obtained of the stop-action video images.

Results

Anatomic 2-dimensional echocardiographic findings and the comparison with angiographic observations are shown in Tables II to IV. As described, an adequate 2-dimensional echocardiographic examination was successfully obtained in 33 of 40 patients (83%).

Atrial-visceral situs: Atrial and visceral situs was determined by 2-dimensional echocardiography, primarily using the location of the liver and the hepatic,





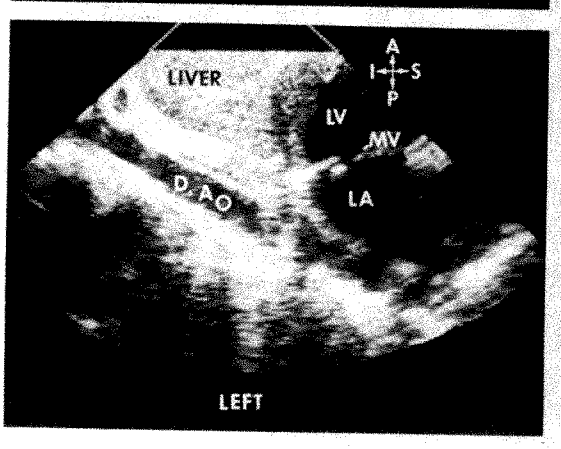


FIGURE 2. Subcostal short-axis (**top left**) and long-axis (**top right and bottom**) scans of inferior vena cava (IVC) and aorta (AO) demonstrate atrial visceral situs. **Top left,** subcostal short-axis scan of the abdomen in 4-month-old boy with situs solitus and isolated dextrocardia. Note that the mass of the liver, hepatic veins (HV), and inferior vena cava lie to the right of the spine while the descending thoracic aorta is visualized slightly to the left. **Top right,** long-axis scan with transducer angulation to the right of the spine demonstrates inferior vena cava and its connection to systemic venous atrium, which is located on the right in 9-year-old patient with situs solitus and isolated dextrocardia. Note that inferior vena cava courses posterior to the body of left ventricle (LV) in order to reach morphologic right atrium (RA). TV = tricuspid valve. **Bottom,** with transducer angulation to the left of the spine, descending abdominal aorta (D.AO) is demonstrated. In addition, the morphologic left atrium (LA) on the left is observed. A separate left atrioventricular valve and the morphologic mitral valve (MV) are also visualized connecting to the morphologic left ventricle. A = anterior; I = inferior; P = posterior; S = superior.

venous, and inferior vena caval connections. Pulmonary venous drainage to the left atrium and coronary sinus drainage, when identified, were used as supportive (secondary) criteria. Atrial-visceral situs was determined by 2-dimensional echocardiography as solitus, inversus, or ambiguous. Once the diagnosis of situs ambiguous was established, no further attempts were made to differentiate atrial situs or morphology based on systemic or pulmonary venous connections.

Atrial-visceral situs solitus was diagnosed when the major portion of the liver, the hepatic veins, and the inferior vena cava were visualized to the right of the spine on short-axis subcostal scans of the abdomen. In addition, the descending abdominal aorta was noted to the left of the spine (Fig. 1 and 2). During a real-time observation, the aorta can be identified by its systolic pulsation and its thicker arterial wall. On long-axis scan with transducer angulation to the right, the inferior vena cava may be observed. Such a long-axis scan of the inferior vena cava demonstrated the hepatic venous connection to the inferior vena cava and the subsequent course of the inferior vena cava to the morphologic right atrium (Fig. 2, top right). A long-axis scan with transducer angulation to the left demonstrated the descending abdominal aorta (Fig. 2, bottom).

Atrial situs inversus was diagnosed when the major portion of the liver, hepatic veins, and inferior vena cava were visualized to the left of the spine on short-axis subcostal scans of the abdomen. In a mirror-image fashion, the descending abdominal aorta was noted to the right of the spine (Fig. 1 and 3). Developing a long-axis scan of the inferior vena cava with transducer angulation to the left emphasized the leftward position of the liver and the hepatic venous connection to the inferior vena cava. The subsequent course of the inferior vena cava was then demonstrated superiorly and to the left-sided systemic venous atrium, the morphologic right atrium (Fig. 3, bottom).

Situs ambiguous was identified when the mass of the liver was midline, equally distributed to the right and to the left.[14] In such cases, the inferior vena cava and abdominal aorta tend to lie on the same side of or directly anterior to the spine, with the inferior vena cava running anterior to the aorta[15] (Fig. 1 and 4). In some cases of situs ambiguous (usually polysplenia), a portion of the inferior vena cava is absent or the inferior vena cava cannot be visualized; in other cases, a hemizygous venous system may be posterior to the aorta but on the same side of the spine (Fig. 4, middle and bottom). Once the diagnosis of situs ambiguous has been established, other noninvasive means may be used to further assess the type—either asplenia or polysplenia.[16]

In this series, 21 of the 33 patients had situs solitus (64%), 9 had situs inversus (27%), and 3 had situs ambiguous (9%). Findings on 2-dimensional echocardiography, cardiac catheterization, and angiography were in agreement in the assignment of situs in all 33.

Apical and subcostal 4-chamber views were used to demonstrate pulmonary venous drainage to the morphologic left atrium and drainage of the coronary sinus

TABLE II Two-Dimensional (2-D) Echocardiography, Segmental Analysis, and Angiographic Correlation in Solitus Group

Case	Sex & Age	AV Con-nection	Ventricular Morphology	Relation of Ventricles and of Rudimentary Pouch to Main Chamber	Ventriculo-arterial Connection	Relation of Arteries (Aorta Position)	Associated Anomalies Defined by 2-D Echo	Angiographic Correlation
1	F, 3 yr	Con	2 ventricles	LV to lt of RV	Con	Rt, post.	Normal	None
2	F, 11 d	Con	2 ventricles	LV to lt of RV	Con	Rt, post.	Normal	None
3	M, 13 yr	Con	2 ventricles	LV to lt and inf. of RV	Con	Rt, ant.	VSD, over-under ventricles, hypoplastic TV (right-sided), and RV, and straddling MV (lt side)	Same
4	M, 9 yr	Con	2 ventricles	LV to lt and ant. of RV	Dis	Rt, ant.	VSD, PS, ASD, juxtaposed atrial appendages	Same
5	M, 4 mo	Con	2 ventricles	LV to lt and ant. of RV	Dis	Rt, ant.	VSD, juxtaposed atrial appendages	Same
6	M, 12 yr	Dis	2 ventricles	LV to rt and post. of RV	DO RV	Lt, ant.	VSD, PS	Same, MV incompetence
7	M, 3 yr	Dis	2 ventricles	LV to rt of RV	SO (aorta) RV, probable pulmonary atresia	Lt, ant.	VSD, lt SVC, confluent pulmonary arteries	Same, pulmonary atresia, lt subclavian to lt PAA, no rt SVC
8	F, 14 yr	Dis	2 ventricles	LV to rt and post. of RV	SO (aorta) RV, probable pulmonary atresia (DO RV)	Ant.	VSD, ASD, confluent pulmonary arteries	Same, large collateral arteries from descending aorta
9	M, 4 yr	Dis	2 ventricles	LV to rt of RV	SO (aorta) RV, probable pulmonary atresia	Not defined	VSD	Same, pulmonary atresia (discordant VA connection), lt juxtaposed atrial appendages
10	M, 12 yr	Dis	2 ventricles	LV to rt of RV	SO (aorta) RV, probable pulmonary atresia	Not defined	VSD	Same, lt ant. aorta
11	F, 7 yr	Dis	2 ventricles	LV to rt of RV	DO RV vs pulmonary atresia	Lt, ant.	VSD, PS, straddling rt AVV, ASD (contrast echo)	Pulmonary atresia, rt subclavian to rt PAA
12	F, 2 yr	Dis	2 ventricles	LV to rt of RV	Probable DO RV	Not defined	VSD, hypoplastic LV, ASD, lt SVC to coronary sinus, absent rt SVC	Same plus multiple muscular defects, aorta directly ant. rt subclavian to rt PAA
13	F, 8 mo	2 AVV (DI)	UVH	OC ant. and to lt of MC	Probably dis	Lt, ant.	Lt AVV chordae inserting in OC	Same, abnormal chordae by echo only
14	M, 21 yr	2 AVV (DI)	UVH	OC ant. and to lt of MC	Dis	Aorta, lt ant.	Severe pulmonary stenosis	Same
15	F, 12 yr	1 AVV (absent rt AV connection)	UVH	OC post. and to rt of MC	DO outlet chamber	Rt, ant.	Atresia of rt AV valve	Previous SVC to rt PAA, lt juxtaposed atrial appendages
16	M, 5 yr	2 AVV (DI)	UVH	OC lt and ant. to LV	Dis	Lt, ant.	Straddling rt AVV to OC	Same
17	M, 29 yr	2 AVV (DI)	UVH	No outlet chamber	DO MC	Lt, ant.	PS, rt AV valve insufficiency (echo contrast)	Indeterminate morphology, small post. pouch

TABLE II (continued)

Case	Sex & Age	AV Connection	Ventricular Morphology	Relation of Ventricles and of Rudimentary Pouch to Main Chamber	Ventriculo-arterial Connection	Relation of Arteries (Aorta Position)	Associated Anomalies Defined by 2-D Echo	Angiographic Correlation
18	F, 9 yr	2 AVV (DI)	UVH	No rudimentary chamber	SO (aorta) ventricle, probable pulmonary atresia	Lt, ant.	Pulmonary atresia	Same, ventricle probable RV morphology with slit-like subpulmonary outlet chamber, pulmonary atresia, lt juxtaposed atrial appendages
19	F, 4 yr	2 AVV (DI)	UVH	No rudimentary chamber	SO (aorta)	Lt	Pulmonary atresia, ASD	Ventricular morphology indeterminate, ascending aorta to rt PAA
20	F, 15 yr	2 AVV (DI)	UVH	No rudimentary chamber	SO (aorta)	Not defined	(?) Pulmonary atresia	Pulmonary atresia
21	M, 14 mo	2 AVV (DI)	UVH	Pouch ant. and to lt of MC	SO (aorta) ventricle (RV)	Lt, ant.	Pulmonary atresia, ASD	Severe valvular and subvalvular PS, UVH RV type with lt ant. pouch

Ant. = anterior; ASD = atrial septal defect; AVV = AV valves; Con = concordant; d = days; DI = double-inlet; Dis = discordant; DO = double-outlet; Inf. = inferior; lt = left; LV = left ventricle; MC = main chamber; MV = mitral valve; OC = outlet chamber; PAA = pulmonary artery anastomosis; Post. = posterior; PS = pulmonary stenosis; rt = right; RV = right ventricle; SO = single-outlet; SVC = superior vena cava; TV = tricuspid valve; UVH = univentricular heart; vs = versus; VSD = ventricular septal defect.

to the morphologic right atrium (Fig. 5). These observations were available as supportive or secondary criteria for recognition of atrial situs. The pulmonary venous connection was correctly identified in 27 of the 33 patients.

Suprasternal scans were used to identify a right- or left-sided superior vena cava, other anomalies of the systemic venous drainage, the drainage of the right pulmonary veins to the left atrium, and the position of the aortic arch. High right parasternal long-axis and subcostal views were employed to demonstrate drainage of the superior vena cava to the right atrium.

Figure 6 (top) demonstrates a normal right superior vena cava in a patient with situs solitus, and Figure 6 (bottom) shows bilateral superior venae cavae in a patient with situs inversus.

AV connection and ventricular morphology: Further assessment of AV connections requires determination of the ventricular morphology. Recently, we

FIGURE 3. Subcostal short-axis (**top**) and long-axis (**bottom**) scans of the abdomen in a 14-year-old patient with situs inversus demonstrate the mass of the liver, hepatic veins (HV,) and inferior vena cava (IVC) coursing to the left of the spine while the abdominal aorta (AO) is observed on the right. A partial long-axis scan (**bottom**) of the inferior vena cava is developed, emphasizing the leftward position of the hepatic venous connection and also the superior course and subsequent drainage of the inferior vena cava into the systemic venous atrium on the left (the morphologic right atrium [RA]).

TABLE III Two-Dimensional (2-D) Echocardiography Segmental Analysis and Angiographic Correlation in Inversus Group

Case	Sex & Age	AV Con-nection	Ventricular Morphology	Relation of Ventricles and of Rudimentary Pouch to Main Chamber	Ventriculo-arterial Connection	Relation of Arteries (Aorta Position)	Associated Anomalies Defined by 2-D Echo	Angiographic Correlation
1	M, 1 mo	Con	2 ventricles	LV to rt of RV	Con	Lt, post.	VSD (small), coarctation of aorta, (?) ASD	Same, patent ductus arteriosus
2	M, 14 yr	Con	2 ventricles	LV to rt and post. of RV	DORV	Lt, post.	VSD, ASD, PS, hypoplastic MV, rt arch	Same
3	F, 3 mo	Con	2 ventricles	LV to rt and inf. of RV	Dis	Rt (side-by-side)	VSD, ASD, straddling lt AV valve	Same, sup.-inf. ventricles
4	F, 14 yr	Con	2 ventricles	LV to rt of RV	Dis (single ventricle)	Ant.	VSD, pulmonary atresia	Same, pulmonary vascular disease
5	M, 16 yr	Dis	2 ventricles	LV to lt of RV	Dis	Rt, ant.	VSD, PS	Same
6	M, 14 yr	Con	2 ventricles	LV postero-inferior	DO RV	Rt (side-by-side)	VSD, straddling lt AV valve	Same
7	M, 6 yr	Con	2 ventricles	LV to rt of RV	Dis	Lt, ant.	Intact ventricular septum, bilateral SVC, ASD	Mild subaortic stenosis
8	F, 12 yr	Common AVV (DI)	UVH	No rudimentary chamber	SO (aorta) ventricle, pulmonary atresia	Rt, ant.	Common atrium, common AV valve, pulmonary atresia (nonconfluent pulmonary arteries visualized), mild AV valve insufficiency (echo contrast)	Same, previous bilateral subclavian to rt and lt pulmonary artery anastomoses
9	M, 10 yr	SI (LAVV atresia)	UVH	Not demon-strated	Not determined	Not defined	Lt Glenn and rt Blalock-Taussig shunts	Same

Ant. = anterior; ASD = atrial septal defect; AVV = AV valves; Con = concordant; DI = double-inlet; Dis = discordant; DO = double-outlet; lt = left; LV = left ventricle; MV = mitral valve; post. = posterior; PS = pulmonary stenosis; rt = right; RV = right ventricle; SI = single-inlet; SO = single-outlet; sup.-inf. = superior-inferior; SVC = superior vena cava; UVH = univentricular heart; VSD = ventricular septal defect.

described the 2-dimensional echocardiographic criteria that were employed to determine ventricular morphology.[6] These criteria require assessment of the AV valve morphology (bileaflet versus trileaflet) (Fig. 7, top), the relative points of attachment of the AV valves to the ventricular septum (the morphologic tricuspid valve attaches lower along the ventricular septum), the presence of 2 papillary muscles for the morphologic left ventricle, and a coarse, heavily trabecular pattern and AV semilunar valve discontinuity for the morphologic right ventricle (Fig. 7, bottom). Thus, in those patients in whom the morphologic right atrium (as determined by atrial situs) connected to the morphologic right ventricle, the AV connection was concordant (Fig. 7, bottom). When the right atrium connected to the morphologic left ventricle, the AV connection was discordant. In this series, 20 patients had 2 separate and well-developed ventricular chambers that could be identified. The morphologic left ventricle was noted to the left and anterior in 6 and to the right and posterior in 14. In 16 patients, a single ventricular septal defect was correctly identified, and in the remaining patients, the ventricular septum was intact.

In all 33 patients, the AV connection was correctly determined. Of the 20 patients with 2 distinct ventricles, 12 had atrial situs solitus, 5 with a concordant AV connection and 7 with a discordant AV connection. Seven patients had atrial situs inversus, and the AV connection was concordant in 6 and discordant in 7. In 1 patient, the atrial situs was ambiguous, with a common AV connection by way of a common AV valve.

Thirteen patients had univentricular heart, 8 with 2 AV valves (double-inlet ventricle), 3 with common AV inlet, and 2 with atresia of 1 AV connection. Two of these patients had situs ambiguous (1 with polysplenia and 1 with asplenia). Four patients had a univentricular heart with an outlet chamber (presumably the anatomic left ventricular type univentricular heart). Three had an outlet chamber that was anterior and to the left. In 1 patient with situs solitus and atretic right AV connections (tricuspid atresia), an outlet chamber was noted posterior and to the right. In 3 patients, a univentricular heart with a rudimentary pouch was observed (presumably the anatomic right ventricular type univentricular heart). In 2, the rudimentary pouch was demonstrated posterior and to the right of the main chamber, and in 1, the pouch was anterior and to the left. In the remaining patients with univentricular heart, the ventricular morphology was indeterminate and a rudimentary or outlet chamber could not be adequately demonstrated echocardiographically.

Ventriculoarterial connections: The ventriculoarterial connections were determined echocardiographically by parasternal long- and short-axis scans (Fig. 7, bottom) and by subcostal long-axis scans (Fig. 8). Identification of the great arteries was based on recognition of the posterior course and early bifurcation of the pulmonary artery and the superior and more anterior course of the aorta. The ventriculoarterial connections were correctly identified in all 20 patients with 2 ventricles. They were concordant in 5 and discordant in 6; 5 patients had double-outlet right ventricle, and 4 had single-outlet (pulmonary atresia) right ventricle. Of the total group, 11 patients were considered to have a single outlet, and pulmonary valve atresia was suspected on the basis of the inability to identify the pulmonary valve or to recognize pulmonary valve motion. Pulmonary valve atresia was confirmed angiographically in 10 of these patients. The relation of the great arteries was not defined in 4 patients with sin-

TABLE IV Two-Dimensional (2-D) Echocardiography Segmental Analysis and Angiographic Correlation in Ambiguous Group

Case	Age (yr) & Sex	AV Connection	Ventricular Morphology	Relation of Ventricles and of Rudimentary Pouch to Main Chamber	VA Connection	Relation of Arteries (Aorta Position)	Associated Anomalies Defined by 2-D Echo	Angiographic Correlation
1	10 M	Common AVV (ambiguous)	2 ventricles	LV to rt post. and inf. of RV	DO RV	Rt, ant.	Common atrium, common AVV, azygous continuation of rt-sided IVC, pulmonary stenosis	LAD coronary arises from rt coronary artery, asplenia
2	6 M	Common AVV (DI)	UVH	Pouch post. and to rt of MC	DO MC	Lt, ant.	Common AV valve, chordae inserting in pouch, azygous continuation of IVC, bilateral SVC, severe PS	Same, polysplenia
3	3 M	Common AVV (DI)	UVH	Pouch post. and to rt of MC	DO MC	Lt, ant.	Common atrium, common AV valve, bilateral SVC, severe PS	Same, previous lt subclavian to lt pulmonary artery and aorta to rt pulmonary artery anastomosis, asplenia

Ant. = anterior; AVV = AV valves; DI = double-inlet; DO = double-outlet; inf. = inferior; IVC = inferior vena cava; LAD = left anterior descending; lt = left; LV = left ventricle; MC = main chamber; post. = posterior; PS = pulmonary stenosis; rt = right; RV = right ventricle; SVC = superior vena cava; UVH = univentricular heart; VA = ventriculoarterial.

gle-outlet ventricle, but the relative position of the great arteries was correctly identified in the remaining 29 patients.

Associated anomalies: Ventricular septal defect was the most common associated anomaly and was present in 16 of the 20 patients who had 2 separate ventricles. The presence of a ventricular septal defect was confirmed by angiography in all 16. Multiple associated muscular ventricular septal defects were identified angiographically in 1 patient. Two-dimensional echocardiography correctly identified the presence of val-

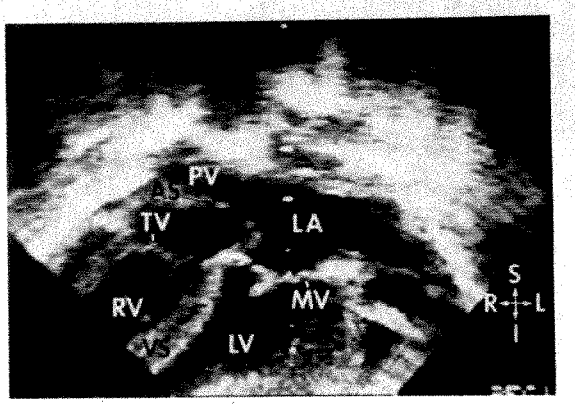


FIGURE 5. Subcostal 4-chamber view in 4-month-old patient with situs solitus and isolated dextrocardia. Pulmonary venous drainage is observed entering the morphologic left atrium (LA) on the left. Ventricular morphology is identified by relative points of insertion of AV valves. Morphologic tricuspid valve (TV) inserts at a lower position along ventricular septum (VS) than morphologic mitral valve (MV). Morphologic left ventricle (LV) has an ellipsoid configuration and a smooth-walled appearance. The left atrium connects with the morphologic left ventricle, with AV concordance. The unusual curved appearance of atrial septum (AS) is partly related to associated left juxtaposed atrial appendages observed in this patient.

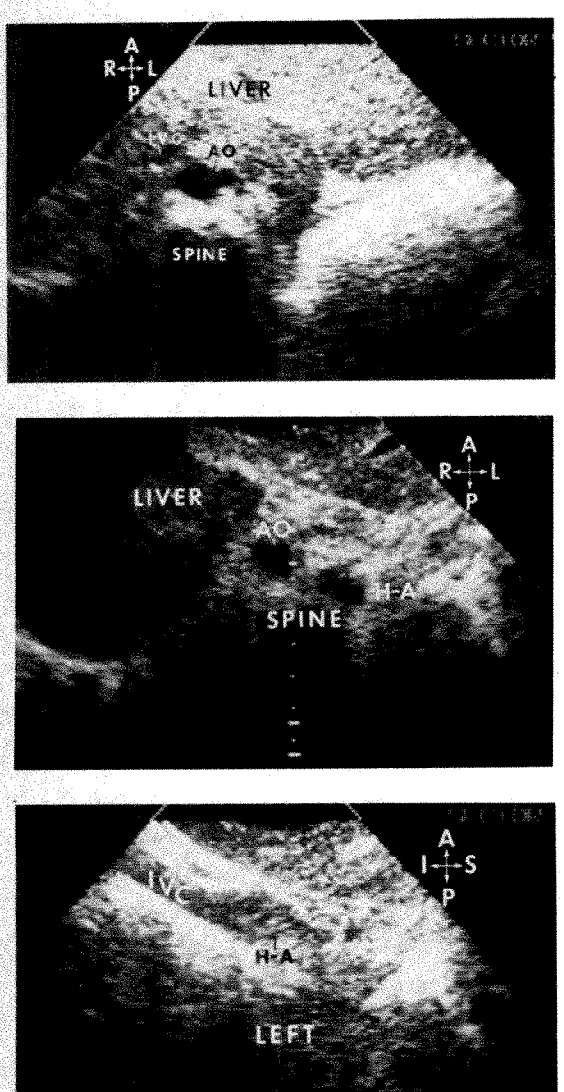


FIGURE 4. Top, subcostal short-axis scan in a patient with situs ambiguous (asplenia), demonstrating a large liver mass centrally located, with nearly equal distribution to right and left of spine. The inferior vena cava (IVC) and aorta (AO) share a central position anteriorly and on the right of the spine. **Middle,** subcostal short-axis scan in patient with situs ambiguous (polysplenia) with hemiazygous (H-A) continuation of the inferior vena cava. In this case, the liver was predominantly located on the right. The aorta was central in position, and the inferior vena cava was on the left. **Bottom,** long-axis scan of the inferior vena cava with transducer angulation to the left demonstrates the abnormal course of the IVC as it begins its hemiazygous continuation to a left superior vena cava.

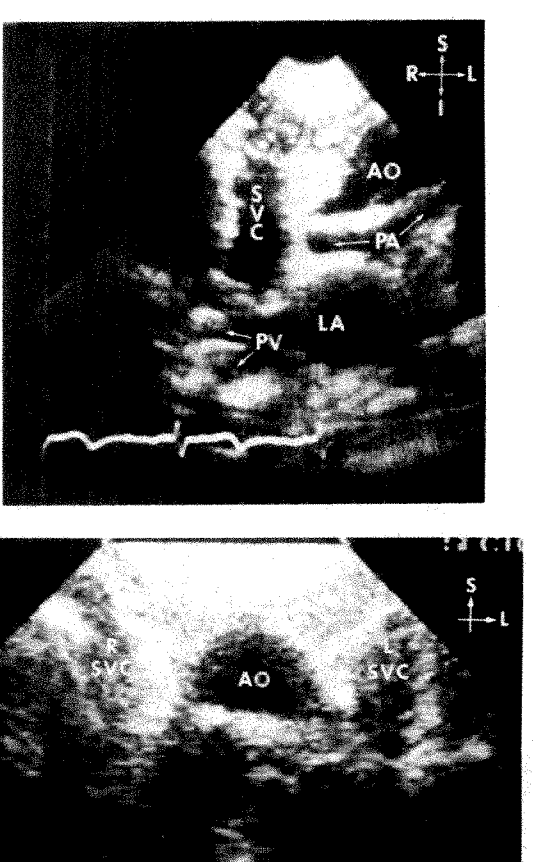


FIGURE 6. Top, suprasternal scan in patient with situs solitus, demonstrating a normally positioned superior vena cava (SVC) coursing to the right of an aortic arch (AO). In addition, inferior to right pulmonary artery (PA) are the left atrium (LA) and right pulmonary veins (PV). **Bottom,** suprasternal scan in patient with situs inversus and bilateral superior venae cavae (RSVC and LSVC). Both superior venae cavae are observed coursing in symmetrical fashion beside the aortic arch. There is no evidence of innominate venous communication between the 2 superior venae cavae.

vular or subvalvular pulmonary stenosis in 8 of the patients. Left juxtaposed atrial appendages were present in 5 patients and were recognized by 2-dimensional echocardiography in 2 of the more recent patients (Fig. 9) (Rice MJ, Seward JB, Hagler DJ, Edwards WD, Julsrud PR, Tajik AJ, submitted for publication).

Discussion

Dextrocardia is a condition in which the major axis of the heart (base to apex) points to the right.[11] The term *dextrocardia* describes only the position of the cardiac axis and does not connote any particular cardiac chamber position, connection, or abnormality. The present study shows that a wide spectrum of congenital heart disease is observed with dextrocardia and can be diagnosed noninvasively.

Segmental analysis of the cardiac anatomy has been employed in the pathologic categorization of dextrocardia by Van Praagh et al,[7] Lev et al,[8] and Calcaterra et al.[9] This method is essential in defining complex cardiac anatomy. A logical approach is to define the situs first and then the AV connection, ventricular morphology, chamber positions, ventriculoarterial connections, relation of the great arteries, and, finally, associated anomalies such as ventricular septal defect or pulmonary stenosis. The cardiac chambers are described as simply anterior or posterior, or left and right of one another. The AV connection can be concordant, discordant, double-inlet, common-inlet, or single-inlet with absence of 1 AV connection. The ventriculoarterial connection can be concordant, discordant, double-outlet, or single-outlet.

The angiographic features of dextrocardia were described by Squarcia et al,[11] thereby applying the segmental approach of dextrocardia to the premortem

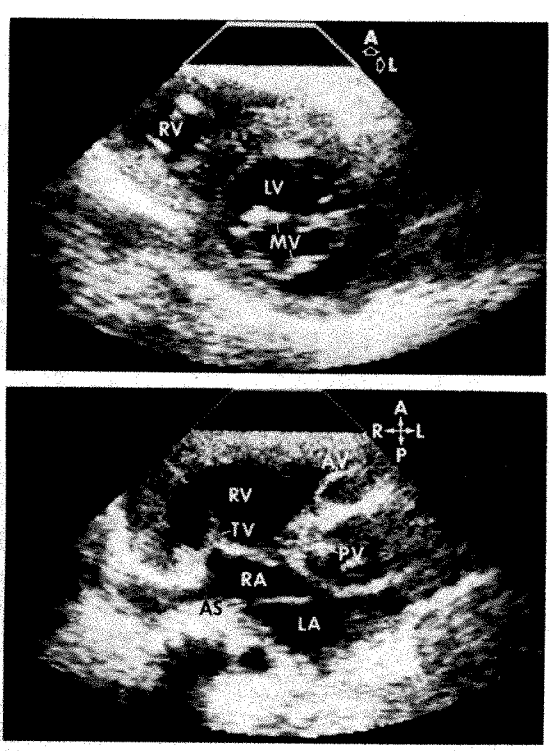


FIGURE 7. Top, short-axis scan of the heart in a 9-year-old patient with situs solitus and isolated dextrocardia. There is AV concordance with the morphologic right ventricle (RV) to the right and anterior and the morphologic left ventricle (LV) to the left and posterior. Morphologic mitral valve (MV) has a typical bileaflet appearance, whereas multiple papillary muscle attachments are observed in the apical portions of the right ventricle. **Bottom,** more superiorly near the cardiac base, the aortic valve (AV) is observed anterior to the pulmonary valve (PV). There is separation of the morphologic tricuspid valve (TV) from the anterior semilunar valve by muscular conus tissue.

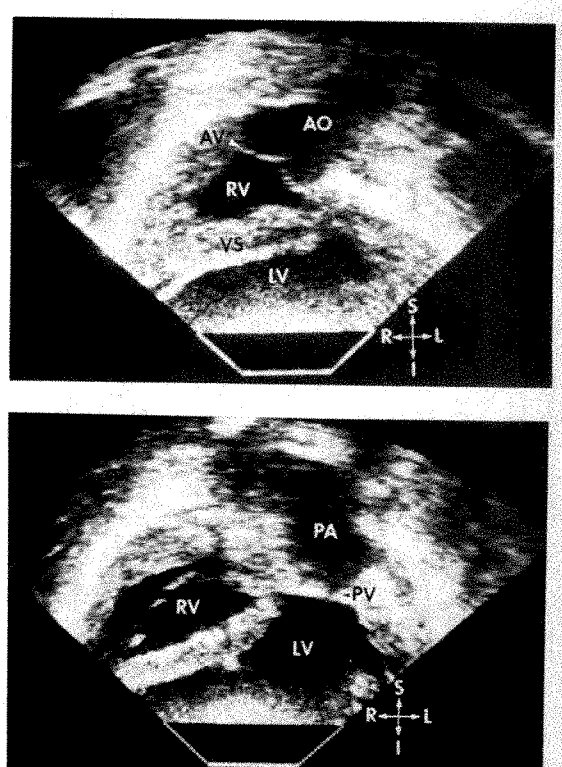


FIGURE 8. Subcostal long-axis scans in the same patient as in Figure 7 demonstrate the origin of the pulmonary artery from the morphologic left ventricle (LV), and with slightly superior transducer angulation, the aortic valve (AV) is observed originating from the morphologic right ventricle (RV)—findings consistent with ventriculoarterial discordance. The pulmonary valve is thickened and domed in this patient with pulmonary valve stenosis.

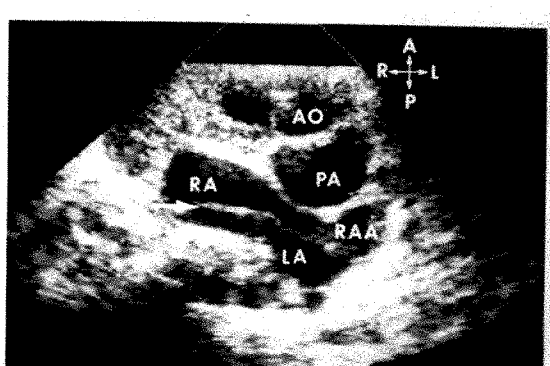


FIGURE 9. Short-axis scan in a patient with isolated dextrocardia and left juxtaposed atrial appendages demonstrates unusual position of atrial septum (**white arrow**) and leftward placement of the right atrial appendage (RAA) behind the pulmonary artery (PA).

patient. They used venoatrial situs plus other clues of situs ambiguous (midline liver, indefinite stomach bubble, symmetric pulmonary vascular pattern, and interrupted or midline inferior vena cava) to define atrial situs. Angiography reliably predicted atrial visceral situs, ventricular morphology, and the relation of the great arteries.

Meyer et al[12] and Solinger et al[13] used M-mode echocardiography to assess noninvasively atrioventricular relationships and arrangement of the great vessels in 12 patients with dextrocardia. Using plain roentgenography of the chest to assess atrial situs as described by Van Mierop et al,[14] they were able to define some important anatomic relations before cardiac catheterization.

In our experience, 2-dimensional echocardiography is vastly superior to M-mode echocardiography in accurately determining the morphology and the position and connection of the cardiac chambers. Wide-angle 2-dimensional echocardiography significantly enhanced spatial orientation and the ability to integrate multiple tomographic sections of the heart during scans. Associated abnormalities such as ventricular septal defect and straddling AV valves can be reliably predicted. When 2 semilunar valves are present, the positions of the great arteries and the ventriculoarterial connection can be confidently defined.

In this study, we attempted to predict situs using findings available only to the echocardiographer. Combining information about the location of the liver and the location and drainage pattern of the inferior vena cava and hepatic veins, we were able to determine noninvasively the correct situs (as determined by cardiac catheterization and angiography) in this series of patients. We also utilized superior vena caval position and drainage, pulmonary venous drainage to the left atrium, and coronary sinus drainage to the right atrium (when identified) as secondary criteria for determination of atrial visceral situs. According to previous studies,[1] the use of venoatrial situs alone is reliable for identifying situs solitus and situs inversus, but is not specific for identifying situs ambiguous. Similarly, we found 2-dimensional echocardiography useful in accurately predicting situs solitus and situs inversus but nonspecific once situs ambiguous was determined. Further studies, including 2-dimensional echocardiographic examination of the pulmonary arterial anatomy with use of suprasternal notch scans and abdominal examination for the presence of a spleen, may be further predictive of bilateral right-sidedness (asplenia) versus bilateral left-sidedness (polysplenia). In addition, computed tomographic scans of the abdomen, as recently reported,[16] appear to be specific for these diagnoses, as are methods that use plain roentgenograms of the chest for determining the bronchial pattern. Presence of Howell-Jolly bodies on peripheral blood smear is also presumptive evidence of asplenia.

Our noninvasive findings agree with those resulting from other methods in previous studies with regard to AV connection in the subgroups of dextrocardia. With dextrocardia and atrial situs solitus, complex congenital heart disease is likely, with both AV discordance and univentricular heart being more common than AV concordance. With dextrocardia and atrial situs inversus, AV concordance is likely; in our series, only 1 patient had AV discordance and 3 had univentricular heart.

Left juxtaposed atrial appendages were present in 5 patients and were diagnosed by 2-dimensional echocardiography in 2. Others[9] have also noted the association between isolated dextrocardia and left juxtaposed atrial appendages.

Two-dimensional echocardiography was compared with angiography; the 2 methods were found comparable (and complementary) with respect to determination of ventricular morphology and definition of the relation of the great arteries. Angiography was superior to echocardiography in defining the ventriculoarterial connections in the presence of pulmonary valve atresia or near-atresia. Two-dimensional echocardiography was clearly superior to angiography in defining the AV valve anatomy and associated abnormalities such as AV valve straddling.

Two-dimensional echocardiography allows the accurate assessment of a number of complex congenital heart defects associated with dextrocardia. Utilizing a segmental approach, one can correctly predict atrial-visceral situs, ventricular morphology and situs, AV connections, and ventriculoarterial connections.

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Conotruncal Malformations: Diagnosis in Infancy Using Subxiphoid 2-Dimensional Echocardiography

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Subxiphoid 2-dimensional echocardiography was performed and interpreted before the first cardiac catheterization in 109 of 113 infants less than 1 year of age with conotruncal malformations, situs solitus of the atria, and d-ventricular loop. The 4 remaining infants could not be examined using this technique for technical reasons.

In 104 of 109 patients successfully examined a correct diagnosis was obtained with the use of subxiphoid 2-dimensional echocardiography. All patients with d-transposition of the great arteries had a correct diagnosis, and in 10 of 11 patients various types of double-outlet right ventricle were recognized by direct visualization of ventriculoarterial connection. Tetralogy of Fallot was correctly diagnosed in 34 of 36 patients and tetralogy of Fallot and pulmonary atresia were correctly diagnosed in 8 of 9 patients, on the basis of the position of the infundibular septum and presence or absence of continuity between the main pulmonary artery and the right ventricle. Five of 6 patients with truncus arteriosus communis were correctly diagnosed by demonstrating a connection between the pulmonary arteries and the ascending portion of the single large semilunar root. Subxiphoid 2-dimensional echocardiography proved to be a sensitive and specific technique for diagnosing conotruncal malformations in infancy.

Malformations of the conotruncus account for 25 to 30% of all congenital heart defects producing serious illness in the first year of life.[1] Included in this category are d-transposition of the great arteries, double-outlet right ventricle, tetralogy of Fallot, tetralogy of Fallot with pulmonary atresia, and truncus arteriosus communis. These lesions usually produce severe derangements of cirulatory physiology, often requiring early diagnosis and intervention to avoid serious morbidity and mortality.

These complex malformations involve 2 separate segments of the heart—the conotruncus and the ventricles. Subxiphoid 2-dimensional echocardiography permits simultaneous visualization of both segments in multiple planes of examination and should be especially useful in diagnosing conotruncal malformations. Since subxiphoid 2-dimensional echocardiography is most applicable in infancy, when patients with these lesions usually are seen, we studied prospectively the accuracy of this technique in diagnosing conotruncal malformations during the first year of life.

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Methods

Study patients: From January 1978 through September 1980 subxiphoid 2-dimensional echocardiography was attempted before the first cardiac catheterization in 128 infants under 1 year of age with conotruncal malformations. Of these, 15 had atrial situs inversus or ambiguous or l-looped (inverted) ventricles and are not included in this report. The remaining 113 infants with situs solitus of the viscera and atria and d-ventricular loop (noninverted ventricles) are the subjects of this report. The ages of the 113 patients ranged from 1 day to 12 months (median 21 days) and their weights from 1.3 to 8.9 kg (median 3.4 kg).

Echocardiography: Subxiphoid 2-dimensional echocardiography was performed with the patients in a supine position, using a Picker Echoview 80 Cardiac Imager with mechanical sector scanner. A 5 MHz short-focused transducer with a 13 mm active element diameter was used for all examinations.[2] The sector arc varied between 45 and 60° with an image rate of 45 to 60/s and a variable line density. All examinations were displayed with inversion of the sector image[3] and were recorded on 0.5 inch videocassette tape. Stop-frame imaging allowed still photographs to be taken using a Tektronics C-50/C-70 series Landpack camera with Polaroid 084 film.

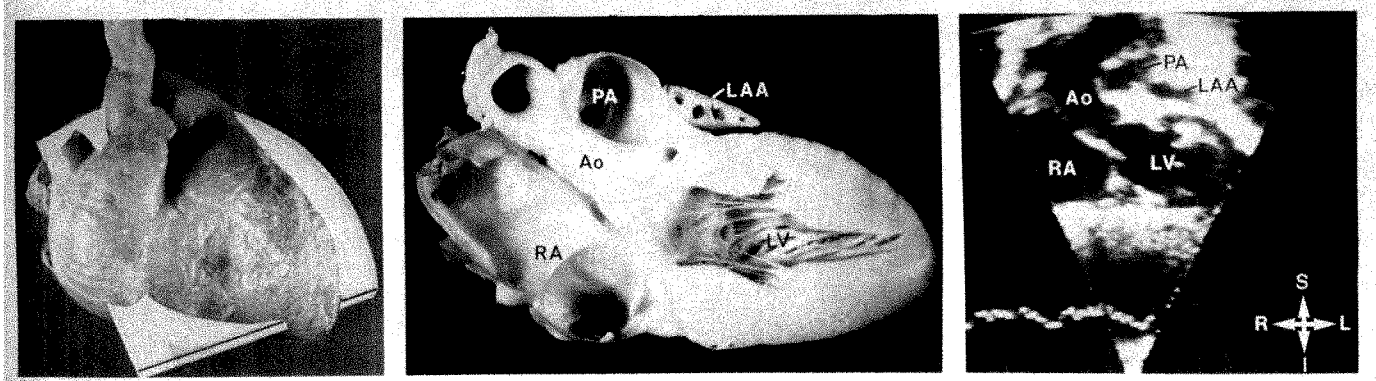

FIGURE 1. Long axis view of left ventricle. **Left,** plane in which the echo beam intersects the heart to generate this view. **Center,** anatomic section of normal heart model cut in this plane. **Right,** subxiphoid 2-dimensional echocardiogram of heart with normally related great arteries. Ao = aorta; I = inferior; L = left; LAA = left atrial appendage; LV = left ventricle; PA = pulmonary artery; R = right; RA = right atrium; S = superior.

Technique: Each echocardiographic examination was begun with the transducer on the subxiphoid area perpendicular to the coronal plane of the trunk. Cranial or anterior (approximately 50°) and leftward (10 to 15°) angulation of the transducer produced a long-axis view of the left ventricle and posterior semilunar root (Fig. 1). A coronal plane view of the right ventricle, right ventricular outflow tract, and anterior semilunar root was obtained with further (60 to 70°) anterior angulation (Fig. 2).

Clockwise rotation (90°) of the transducer about its long axis produced a transverse or cross-sectional view of the heart. While multiple transverse planes were examined,[2] 2 were particularly useful in diagnosing conotruncal malformations. Angling the transducer toward the left sternoclavicular joint displayed a transverse section of the base of the ventricles, the origin of the rightward semilunar root, and the membranous and atrioventricular canal portions of the interventricular septum (transverse plane A, Fig. 3). Additional angulation toward the medial third of the left clavicle displayed the left-sided semilunar root, the infundibular septum, and the mid-muscular septum (transverse plane B, Fig. 4).

Cardiac catheterization: Conotruncal anatomy was displayed using biplane cineangiography, including standard anteroposterior and lateral projections as well as various angled oblique views,[4] and was described using the nomenclature of van Praagh and co-workers.[5,6]

Data analysis: The echocardiography was performed and the results were interpreted by the echocardiographer before cardiac catheterization. The cineangiograms were reviewed and interpreted by the cardiovascular radiologist. Routine clinical data, including physical examination, chest x-ray, electrocardiogram, and arterial blood gases, were available to both. Cineangiographic diagnoses were accepted as correct for purposes of scoring the echocardiographic results.

Results

Subxiphoid 2-dimensional echocardiography was successfully performed as the primary diagnostic procedure in 109 of the 113 infants with conotruncal malformations associated with atrial situs solitus and d-ventricular loop (noninverted ventricle). In 4 patients, an adequate subxiphoid 2-dimensional echocardiographic examination could not be performed because of poor patient cooperation (2), recent abdominal surgery (1), and marked pulmonary hyperexpansion in 1 patient with absent pulmonary valve syndrome. The atrial situs and ventricular loop were correctly deter-

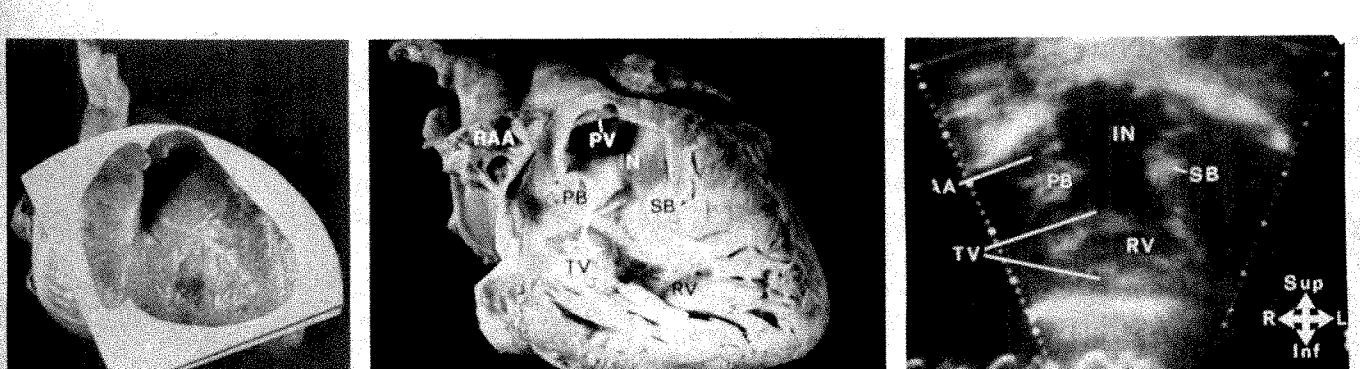

FIGURE 2. Coronal plane view of right ventricle. **Left,** plane in which the echo beam intersects the heart to generate this view. **Center,** anatomic section of normal heart cut in this plane. **Right,** subxiphoid 2-dimensional echocardiogram of heart with normally related great arteries. IN = infundibulum; PB = parietal band; PV = pulmonary valve; RV = right ventricle; SB = septal band; TV = tricuspid valve. Other abbreviations as in Figure 1.

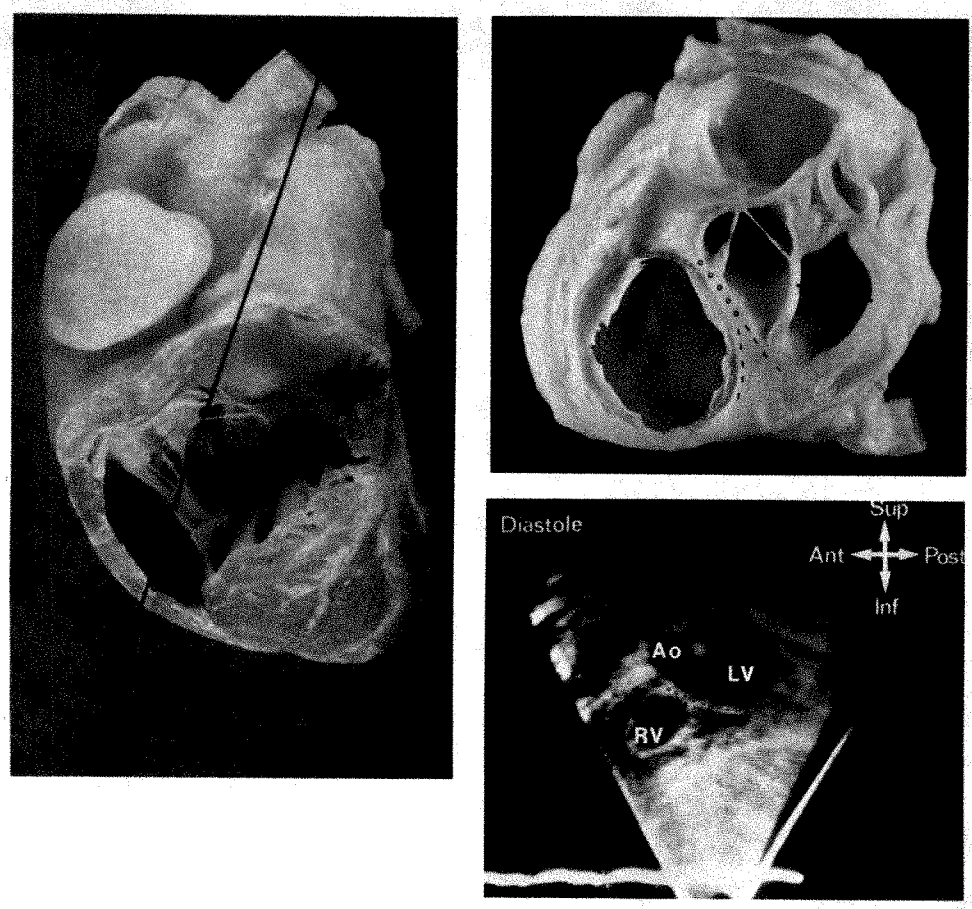

FIGURE 3. Transverse plane A, a transverse section through the base of the ventricles, the rightward semilunar root, and the membranous (**circles**) and atrioventricular canal (**dashed line**) portion of the interventricular septum. **Left,** plane in which the echo beam intersects the heart to generate this view. **Right,** anatomic section of a normal heart model cut in this plane. **Bottom,** subxiphoid 2-dimensional echocardiogram of a heart with normally related great arteries. AML = anterior mitral leaflet; Ant = anterior; Post = posterior; other abbreviations as before.

mined in all 109 patients. (Thirteen of the other 15 patients with conotruncal malformations associated with atrial situs inversus or ambiguous or l-ventricular loop [inverted ventricles] were also correctly identified prospectively using subxiphoid 2-dimensional echocardiography. The ventricular loop could not be determined echocardiographically or angiographically in the 2 remaining patients with single ventricular chamber.) The correct diagnosis was made in 104 (95%) of the 109 patients successfully examined using subxiphoid 2-dimensional echocardiography (Table I).

D-transposition of the great arteries (Fig. 5): All 46 patients with d-transposition of the great arteries were correctly identified prospectively on the basis of great artery morphology and direct visualization of ventriculoarterial connections.[3] There were no false-positive diagnoses.

An intact interventricular septum was correctly diagnosed in 19 of 20 patients and a ventricular septal defect was recognized in 16 of 23 patients (68%) by subxiphoid 2-dimensional echocardiography. Seven false-negative reports were issued in patients with trivial muscular (5) or membranous (1) ventricular septal defects which were hemodynamically insignificant and did not influence management. Three of 46 patients had tricuspid atresia with transposition of the great arteries; all were correctly diagnosed by echocardiography.

The only associated lesion which complicated the diagnosis of d-transposition of the great arteries was a malalignment ventricular septal defect (that is, a defect associated with anterior placement of the infun-

TABLE I Subxiphoid 2-Dimensional Echocardiographic Results by Diagnostic Category

	Angiography	Correctly Diagnosed by Echocardiography	Errors
Transposition of the great arteries	46	46	0
Double-outlet right ventricle	12	11	1
Tetralogy of Fallot	36	34	2
Tetralogy of Fallot and pulmonary atresia	9	8	1
Truncus arteriosus communis	6	5	1
Total	109	104	5

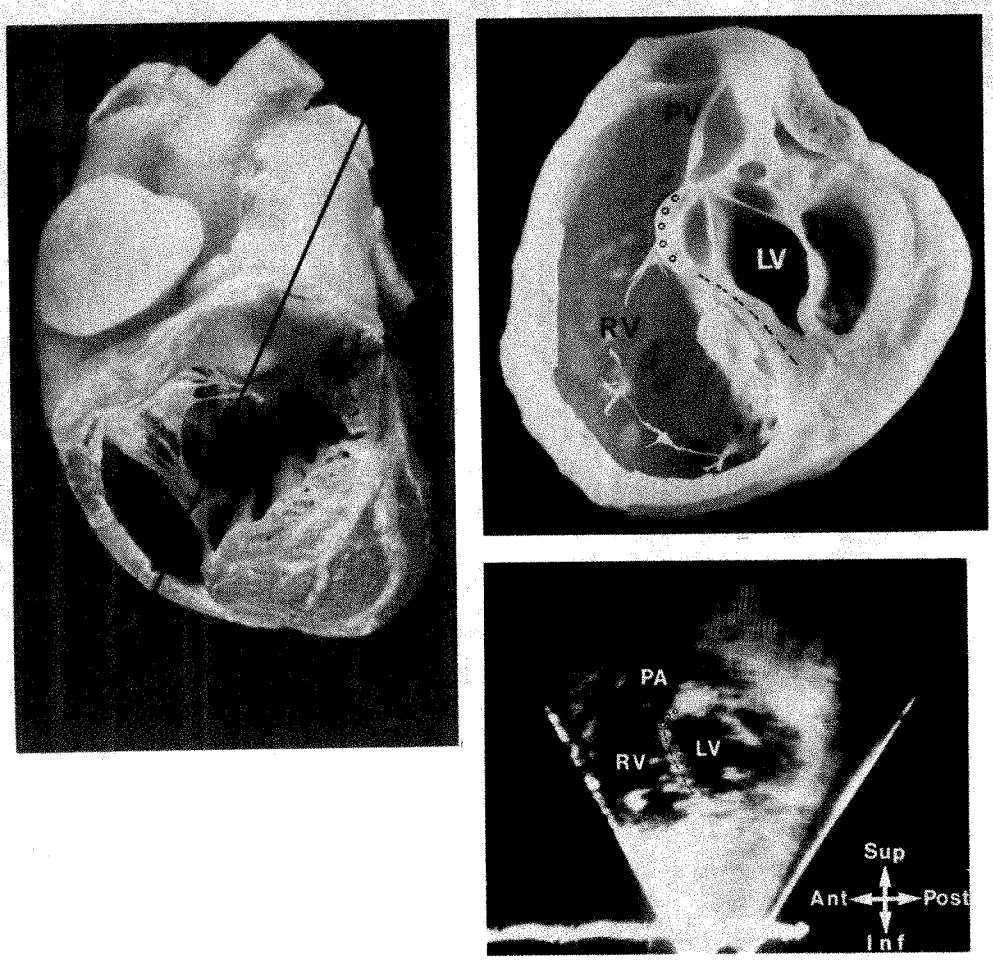

FIGURE 4. Transverse plane B, transverse plane through the left-sided semilunar root, the infundibular septum (**circles**) and the mid-muscular interventricular septum (**dashed line**). **Left,** plane in which the echo beam intersects the heart to generate this view. **Right,** anatomic section of normal heart model cut in this plane. **Bottom,** subxiphoid 2-dimensional echocardiogram of heart with normally related great arteries. Abbreviations as before.

dibular septum allowing the posterior semilunar root to override the interventricular septum[7]) in which the pulmonary artery straddled the interventricular septum symmetrically (2 of 5 patients with d-transposition of the great arteries and malalignment ventricular septal defect), making differentiation between d-transposition of the great arteries and double-outlet right ventricle difficult. Apparent continuity between the mitral and pulmonary valves as well as a difference in the heights of the semilunar valves (pulmonary inferior and aortic superior) suggested the diagnosis of d-transposition of the great arteries in both patients. One of these 2 patients died at the time of the intracardiac repair. Postmortem examination revealed a small (approximately 2 mm) strip of muscle (conus) between pulmonary and mitral valves. However, the relation between the pulmonary artery and the ventricles was ambiguous.

Double-outlet right ventricle (Fig. 6): This anomaly was correctly diagnosed in 11 of 12 patients on the basis of great artery position with respect to the interventricular septum. The origin of at least "1½" great arteries from the right ventricle, as demonstrated in the coronal plane of the right ventricle or transverse plane A or B, or both, was considered diagnostic of double-outlet right ventricle.[8–12] While the origins of side-by-side semilunar roots were well seen in the coronal plane view of the right ventricle, the identity of each root could best be determined using the transverse planes. The only patient with double-outlet right ventricle incorrectly diagnosed by subxiphoid 2-dimensional echocardiography had a small ascending aorta associated with severe coarctation and a large patent ductus arteriosus. The main pulmonary artery and ductus arteriosus (which were continuous with the descending aorta) were mistaken for the ascending and transverse aorta. The ascending aorta was small and not recognized. This led to the incorrect diagnosis of d-malposition of the great arteries with pulmonary atresia.

Double-outlet right ventricle was correctly characterized in 11 of 11 patients on the basis of the relative position of the great arteries, the degree of subsemilunar narrowing, the position of the ventricular septal defect, and the status of the mitral valve and left ventricle. In 6 patients the aorta was to the right and posterior with a subaortic ventricular septal defect (tetralogy of Fallot

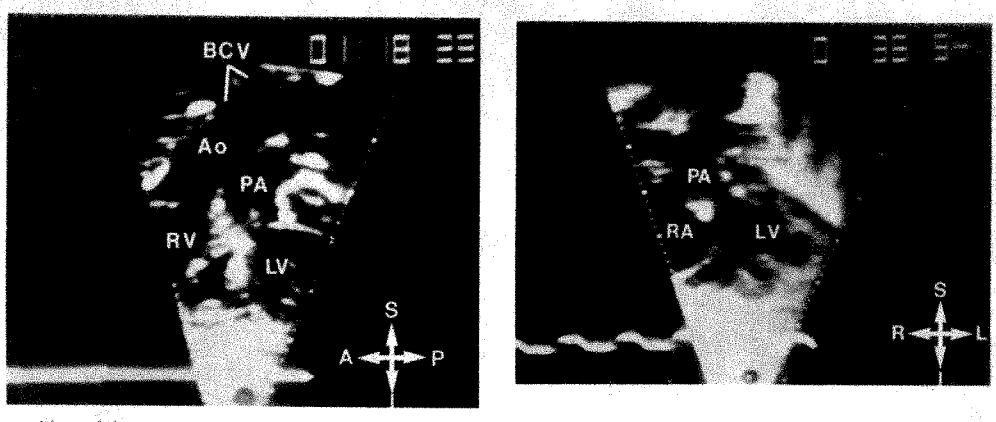

FIGURE 5. D-transposition of the great arteries. **Left,** long axis view of left ventricle. The posterior pulmonary artery (PA) is identified by bifurcation into branch pulmonary arteries. **Right,** transverse plane A. The arch-forming aorta (Ao) arises from the anterior right ventricle (RV). Superior border of the arch is broken by origins of the brachiocephalic vessels (BCV). P = posterior; other abbreviations as before.

type). Narrowing of the subpulmonary area was identified in 5 of the 6. The great arteries were relatively side by side with a rightward aorta in 3 patients; the ventricular septal defect was subpulmonary in 2 (Taussig-Bing type) and uncommitted in 1. The other 3 patients had double-outlet right ventricle associated with mitral atresia or severe mitral stenosis and hypoplasia of the left ventricle.

The relative positions of the great arteries were determined from the orientation of the transducer in a plane which displayed both great arteries simultaneously. Subsemilunar narrowing was assessed qualitatively from multiple sweeps of the outflow tracts in both transverse and coronal planes. The position of the ventricular septal defect relative to the great arteries was determined by identifying which great artery was closer to the defect in 1 of the transverse planes. If neither of the great arteries could be imaged in the same transverse plane as the ventricular septal defect, it was considered uncommitted. The status of the mitral valve and left ventricle was determined from multiple transverse and long axis views.

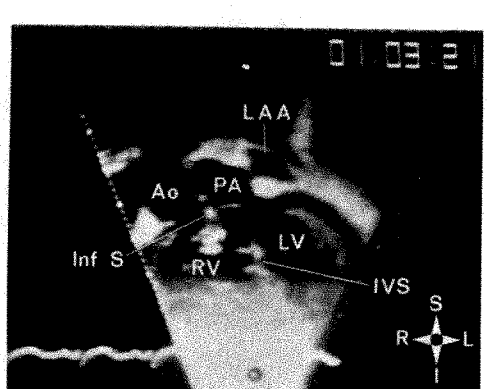

FIGURE 6. Coronal plane of right ventricle in case of double-outlet right ventricle. Both great arteries (Ao and PA) arise above the right ventricle (RV); the identity of the great arteries can not be determined in this view. IVS = interventricular septum; abbreviations as before.

Tetralogy of Fallot (Fig. 7): Thirty-four of 36 patients with tetralogy of Fallot were correctly diagnosed by subxiphoid 2-dimensional echocardiography. The criteria used were (1) anterior displacement of the infundibular septum associated with subpulmonary narrowing and a malalignment ventricular septal defect with overriding aortic root, and (2) a demonstrable pulmonary valve and continuity between the right ventricular outflow tract and the main pulmonary artery.[8–12] One patient, early in our experience, was incorrectly diagnosed as having a membranous ventricular septal defect without right ventricular outflow tract obstruction. The other patient misdiagnosed in this group was thought to have tetralogy of Fallot and pulmonary atresia after subxiphoid 2-dimensional echocardiography, whereas cineangiography showed a severely stenotic right ventricular outflow tract. Thus, in 35 of 36 patients with tetralogy of Fallot, a pulmonary valve and a patent right ventricular outflow tract could be demonstrated.

Tetralogy of Fallot and pulmonary atresia (Fig. 8): Eight of 9 patients with tetralogy of Fallot and pulmonary atresia were correctly diagnosed using subxiphoid 2-dimensional echocardiography by demonstrating (1) a large aortic root overriding the interventricular septum through a malalignment ventricular septal defect (with no demonstrable pulmonary valve and outflow tract), and (2) no direct connection between the pulmonary arteries and the ascending aorta. The diagnostic error in this category resulted from mistaking the left atrial appendage for the proximal main pulmonary artery, leading to the diagnosis of tetralogy of Fallot with a patent outflow tract.

Truncus arteriosus communis (Fig. 9): Truncus arteriosus communis was correctly diagnosed in 5 of 6 patients. The diagnostic criteria were (1) a single semilunar root overriding the interventricular septum through a malalignment ventricular septal defect, and (2) direct continuity between 1 or both pulmonary arteries and the ascending portion of the single semilunar root. In all 5 patients correctly diagnosed the truncal

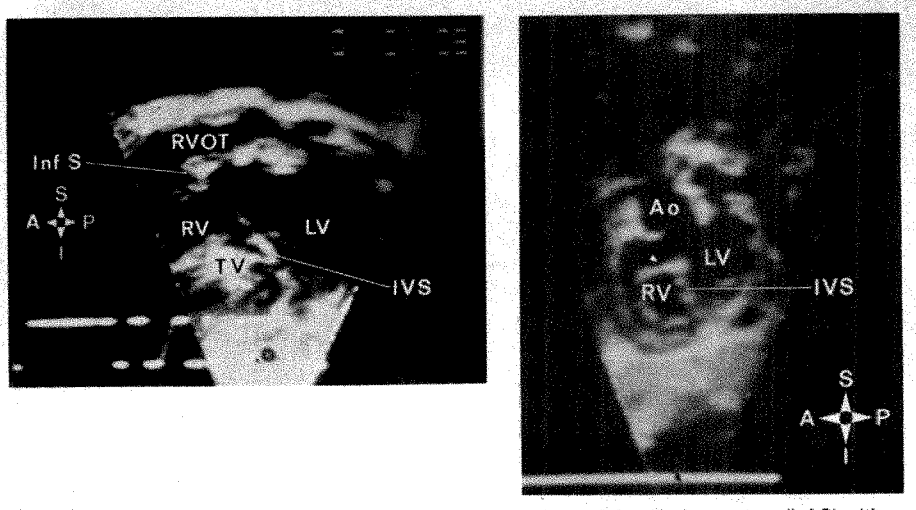

FIGURE 7. Tetralogy of Fallot. **Left,** transverse plane B showing the anteriorly displaced infundibular septum (Inf S) with narrowed right ventricular outflow tract (RVOT) and malalignment ventricular septal defect (IVS). **Right,** transverse plane A showing the dilated aorta (Ao) overriding the interventricular septum. The malalignment ventricular septal defect is below the aortic valve and above the superior septal attachments of the tricuspid valve (**white arrow**). A = anterior; other abbreviations as before.

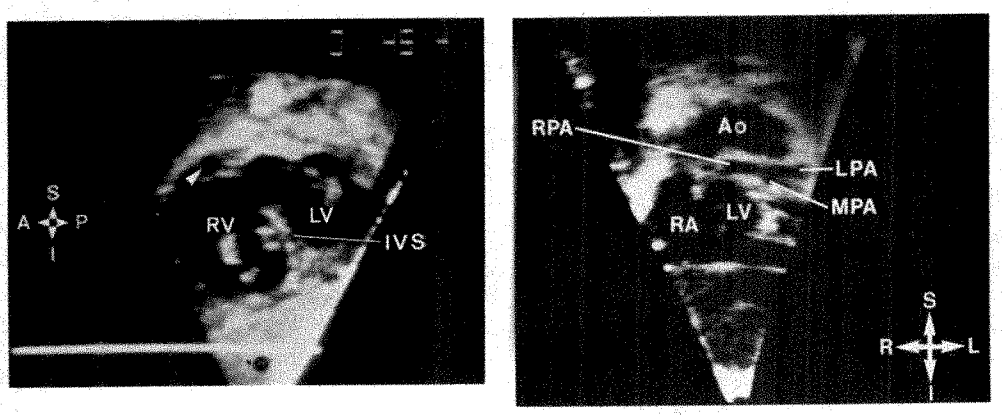

FIGURE 8. Tetralogy of Fallot with pulmonary atresia. **Left,** transverse plane B. The blindly ending right ventricle outflow tract (**white arrow**) is seen in this view. Continuity between the right ventricle (RV) and the pulmonary artery can not be demonstrated by scanning to either side of this plane. **Right,** caudal angulation from the long axis of the left ventricle (LV) displays confluence of the branch pulmonary arteries (RPA and LPA). The main pulmonary artery (MPA) ends proximally as a blind diverticulum (gull-wing appearance). Abbreviations as before.

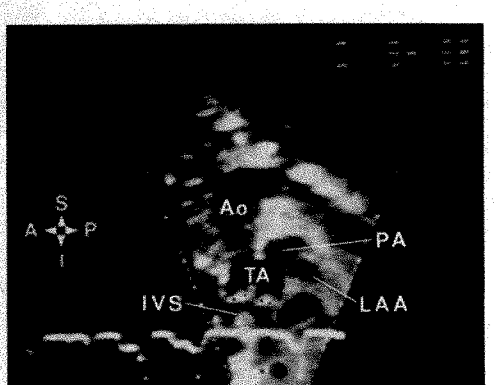

FIGURE 9. Transverse plane A in truncus arteriosus communis Type I-A. The truncal valve (**dotted line**) is large and thickened. The aortopulmonary septum is seen distally dividing the truncus (TA) into its aortic (Ao) and pulmonary artery (PA) portion. Abbreviations as before.

valve was large; in 4 it appeared thickened and dysplastic with an eccentric orifice. The sixth patient was incorrectly diagnosed as having double-outlet right ventricle after a limited examination. Poor visualization of the anterior portion of the right ventricle led to the false impression that a second outflow tract was present.

Discussion

Subxiphoid 2-dimensional echocardiography proved to be a sensitive and specific method for diagnosing conotruncal malformations. The only specific limitation to its use was an abnormality of the abdominal wall restricting transducer placement. We found that multiple plane imaging, facilitated by the broad acoustical window of the subxiphoid space, was extremely important in diagnosing these complex cardiac malformations.

Imaging in multiple coronal and transverse planes allowed a more precise description of the spatial orientation of the various structures.

Potential for diagnostic error: We believe that the ability to display the ventricles and the great arteries simultaneously is a further advantage of subxiphoid 2-dimensional echocardiography in diagnosing conotruncal malformations. The identity of each great artery can be determined on the basis of its morphologic features and its ventricular connections can be directly visualized. While a potential source of error peculiar to this approach is misidentification of a great artery (as in our case of double-outlet right ventricle incorrectly diagnosed), our experience suggests that careful attention to the morphologic criteria for great artery identification[3] should virtually eliminate this problem.

Since all structures are viewed in more than 1 plane, with less than 1 mm axial and less than 2 mm lateral resolution, difficulties resulting from false drop-out or superimposition of adjacent structures occurred rarely and led to diagnostic errors in only 2 patients; 1 patient had tetralogy of Fallot with pulmonary atresia and the other had truncas arteriosus communis.

Problems with resolution caused only 1 significant error in diagnosis. A single patient with tetralogy of Fallot was misdiagnosed as having tetralogy of Fallot with pulmonary atresia because the right ventricular outflow tract was not visualized with our equipment. Such narrowed anterior outflow tracts challenge the resolving power of even high frequency, wide active element diameter transducers with excellent axial and lateral resolution. Perhaps other methods such as Doppler echocardiography[13] will improve diagnostic accuracy in such situations.

Clinical applications: To determine the clinical utility of subxiphoid 2-dimensional echocardiography in the diagnosis of conotruncal malformations in infants we attempted to approximate the usual clinical setting in the design of the study. Thus, the echocardiographer was aware of the physical and laboratory findings while performing and interpreting the subxiphoid 2-dimensional echocardiographic examination. While a complete echocardiographic examination was performed in virtually all cases, the clinical information may have allowed the examiner to focus on areas of interest suggested by the clinical data.

Under the conditions of our study, subxiphoid 2-dimensional echocardiography, using multiple planes of examination, proved to have a diagnostic accuracy similar to that of contrast angiography. Although other types of conotruncal malformations (for example, l-transposition or other types of l-looped or inverted ventricles) were excluded for the sake of brevity and unity, inclusion of such lesions would have little effect on the results. Nonetheless, in our own practice subxiphoid 2-dimensional echocardiography has not replaced cardiac catheterization and angiography on a routine basis. Rather, the 2 methods are used in a complementary fashion: echocardiography is used to screen patients suspected of having congenital heart disease and to provide a general diagnosis; cardiac catheterization and angiography are then applied, as needed, to supply physiologic data and anatomic details not demonstrable with echocardiography.

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Two-Dimensional Echocardiographic Assessment of Right Ventricular Volume in Children With Congenital Heart Disease

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The ability of 2-dimensional echocardiography to measure right ventricular (RV) volume and ejection fraction was assessed in 22 children with congenital heart disease. From the apical 4 chamber 2-dimensional echocardiographic image, the long-axis length of the right ventricle was measured and the area planimetered. On the anteroposterior and lateral cineangiocardiographic planes, the right ventricle was separated into 2 parts: RV sinus and outflow tract. The longest length, inflow tract length, and area of the sinus were measured from biplane cineangiographic views. The echographic long-axis length correlated well with the longest length of the RV sinus measured from both anteroposterior and lateral cineangiographic views at both end-systole and end-diastole. Moreover, the echographic area correlated well with the sinus area obtained from both cineangiographic views. From these regression analyses, the echographic long axis length and area were corrected to the angiographic longest length and area of the sinus. The new corrected echographic longest length and area were applied to 3 formulas (2 biplane and 1 uniplane) to calculate the sinus volume of the right ventricle. Total RV volume was then derived from the sinus volume. RV volumes and ejection fraction determined by 2-dimensional echocardiography were compared with those obtained from biplane cineangiography using Simpson's rule method. All formulas tested predicted RV volumes and ejection fraction with equal accuracy. Thus, 2-dimensional echocardiography can assess RV volume and ejection fraction in children with congenital heart disease.

RV dimension from M-mode echocardiographic images has been used to identify patients with RV volume overload[1-4] but cannot be used to determine RV volume. Recently, the 2-dimensional echocardiographic apical 4-chamber image has been employed to measure RV dimensions and area.[5,6] Bommer et al[5] showed that the RV area and minor axis length correlated well with the volume of RV casts. The use of computer analysis of 2-dimensional echocardiographic images has facilitated the noninvasive evaluation of left ventricular volumes and ejection fraction in adults[7-9] and children.[10,11] To date, however, determination of RV volumes by 2-dimensional echocardiography has been achieved only in adults with chronic obstructive lung disease[12] and in children with complete transposition of the great arteries after Mustard's procedure.[13] We have introduced a simplified angiographic area-length method for estimating RV volumes[14] (see Appendix). The present study was therefore undertaken to assess the accuracy of RV volume determination in infants and children with congenital heart disease by application of the new simplified area-length method to cross-sectional echocardiographic images.

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Methods

Study patients: Twenty-two consecutive patients scheduled for diagnostic cardiac catheterization and 2-dimensional echocardiography were entered into the study. The clinical diagnoses are summarized in Table I. Ages ranged from 1

TABLE I Patient Data

Diagnosis	Patients (n)	Age Range (yr)
Normal heart	2	0.6, 8.0
Atrial septal defect	4	1.0–3.0
Atrial septal defect (postop)	1	0.9
Cardiomyopathy	1	0.8
LV-RA communication	1	4.0
Tetralogy of Fallot	2	3.0, 5.0
Total anomalous pulmonary venous return	2	0.8, 0.8
Transposition of great vessels (postop)	2	2.0, 3.0
Valvular pulmonary stenosis	2	5.0, 11.0
Ventricular septal defect	5	0.16–8.0

LV-RA = left ventricular-right atrial; postop = postoperatively.

month to 11 years (mean 2.9) and body surface area ranged from 0.18 to 1.3 m^2 (mean 0.52). All patients underwent 2-dimensional echocardiographic examination within 24 hours of cardiac catheterization.

Echocardiography: Echocardiographic studies were performed using a commercially available phased array sector scan (Toshiba SSH-10A). A transducer composed of 32 piezoelectric crystals (2.4 MHz) which were dynamically focused was employed. The echographic beam was steered electronically through a 78° sector arc. The focal point was adjusted to 4.5 or 7.5 cm depending on the size of the patient. Axial and lateral resolution was established by an ultra-Cal standard 100 mm test object phantom box. Axial resolution was 1 mm at any depth and lateral resolution was 1.5 to 2 mm at and before the focal point. At 2 cm from the focal point, lateral resolution became 2.5 mm, and at 5 cm from the focal point, it became 3 mm.

The apical 4-chamber image was obtained with the head of the patient slightly elevated and the patient in a 45° left lateral decubitus position. The transducer was applied to the apex and the sector fan directed to the right shoulder.[15] Care was taken to record a clear endocardial image by optimizing gain settings. The images were recorded on videotape at 30 frames/s (Nipon Electric, Tokyo, Japan) for later playback and analysis in the stop-motion mode. From the apical 4-chamber 2-dimensional echographic view, the long-axis length and area of the right ventricle were measured at end-systole and end-diastole (Fig. 1). The long-axis length was measured from the apex to the center of the tricuspid valve. The area of the right ventricle was traced on transparent onlay paper from the endocardial surface of the right ventricle through the plane of the tricuspid valve. When small defects in the endocardial echoes were observed, the area of outline was completed by a straight line between adjacent clear endocardial echoes. The area was then calculated by means of a graphic image analyzer (Neumonics, Philadelphia, Pennsylvania) interfaced with a minicomputer (Wang, Tewksbury, Massachusetts).

An attempt was made to determine the timing of end-systole and end-diastole for echocardiographic measurements. In 14 patients in whom tricuspid valve motion was clearly defined on the apical 4-chamber image, the long-axis length and area of the right ventricle were obtained by using closure and opening of the tricuspid valve as end-diastole and end-systole, respectively. These measurements were also obtained by using the onset of the QRS complex of the reference electrocardiogram as end-diastole and the end of the T wave as end-systole.

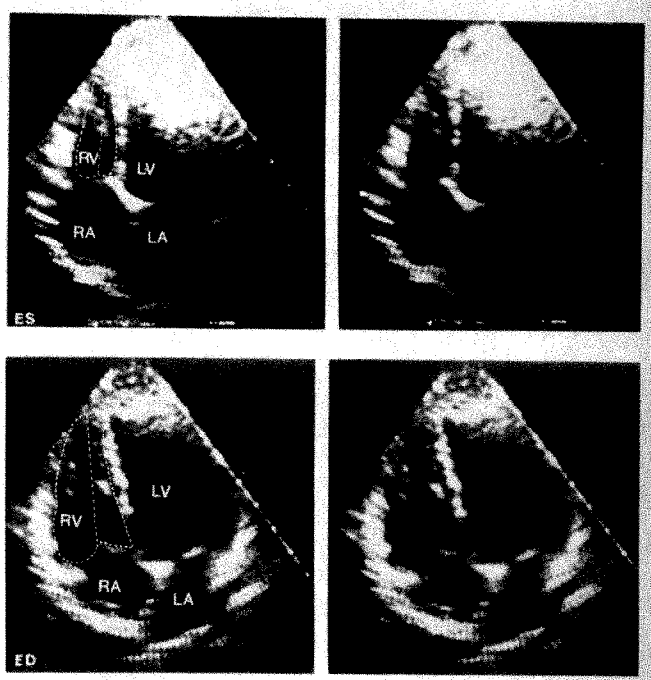

FIGURE 1. Two-dimensional echocardiogram in the apical 4-chamber view. **Top,** at end-systole (ES); **bottom,** end-diastole (ED). From this view the area (**dotted line** along the endocardial surface) of the right ventricle (RV) was planimetered and length (**dotted line** from apex to tricuspid valve) measured. LA = left atrium; LV = left ventricle; RA = right atrium.

Angiocardiography: Biplane cineangiocardiography was performed in the anteroposterior and lateral projection at 60 frames/s after injecting 1.0 to 1.25 ml/kg of body weight of 76% Renografin® into the right atrium or the right ventricle. The patient was always in the supine and horizontal position. Only sinus beats were used to measure RV dimensions and volumes. The right ventricle was separated into 2 parts, the RV sinus and outflow tract, by constructing a horizontal line on both cineangiographic views[16] (Fig. 2). RV end-diastolic and end-systolic volumes were calculated using the Simpson's rule method.[17] *Right ventricular ejection fraction (RVEF) was calculated by the equation:* RVEF = (RVEDV − RVESV)/RVEDV, where RVEDV is right ventricular end-diastolic volume and RVESV is right ventricular end-systolic volume.

The following measurements were also obtained from biplane cineangiographic images of the right ventricle at end-diastole and end-systole: (1) RV inflow length = the distance from the apex of the right ventricle to the mid-tricuspid valve; (2) the longest length of the RV sinus = the longest distance from the apex to any portion of the tricuspid valve; and (3) the RV sinus area.

Corrected echocardiographic measurements: The RV length and area measurements obtained from 2-dimensional echocardiography were compared with the variables obtained from both anteroposterior and lateral cineangiographic views. From these regression equations, we derived the corrected echographic longest length of the right ventricle. In a similar fashion, the corrected echographic area was also derived. These corrected values were then used to calculate RV sinus volume. Total RV volume was calculated from the sinus volume of the right ventricle in 20 patients without tetralogy of Fallot by the following equations: *Method I* = TRVV = 1.061 × $(CEA_{AP} \times CEA_{LAT})/CELL_{AP}$; *Method II* = TRVV = 0.849

TABLE II Timing of End-Systole and End-Diastole

	End-Systole					End-Diastole				
	At End of T wave		At Opening of TV			At Onset of QRS Wave		At Closing of TV		
Variable	Mean	SD	Mean	SD	P	Mean	SD	Mean	SD	P
Length (cm)	3.3	0.94	3.1	0.97	0.1	4.5	1.3	4.4	1.3	0.1
Area (cm^2)	4.7	2.6	4.5	2.4	0.1	8.3	3.5	8.4	3.7	0.1

SD = standard deviation; TV = tricuspid valve.

$\times (CEA_{AP} \times CEA_{LAT})/CELL_{LAT}$; and *Method III* = TRVV $= 1.316 \times (CEA_{LAT})^2/CELL_{LAT}$, where TRVV = total RV volume, CEA = corrected echographic area, CELL = corrected echographic long-axis length, AP = anteroposterior cineangiogram, and LAT = lateral cineangiogram. In the 2 patients with tetralogy of Fallot, total volume was obtained by using the constants 0.981, 0.785, and 1.217 for Methods I, II, and III, respectively.

Statistics: Linear regression analysis was performed using the least-squares method. The standard error of the estimate was calculated using the standard deviation. The difference beween the regression equation for the 3 methods was determined by testing the variance, slope, and Y intercept using analysis of covariance.[18] Student's *t* test was used to test the difference between the means in heart rate and timing of end-systole and end-diastole. The difference was statistically significant when the p value was less than 0.05.

Results

The heart rate during angiography (121.8 ± 28 beats/min, mean ± standard deviation) and 2-dimensional echocardiography (113.7 ± 33 beats/min) was not statistically different.

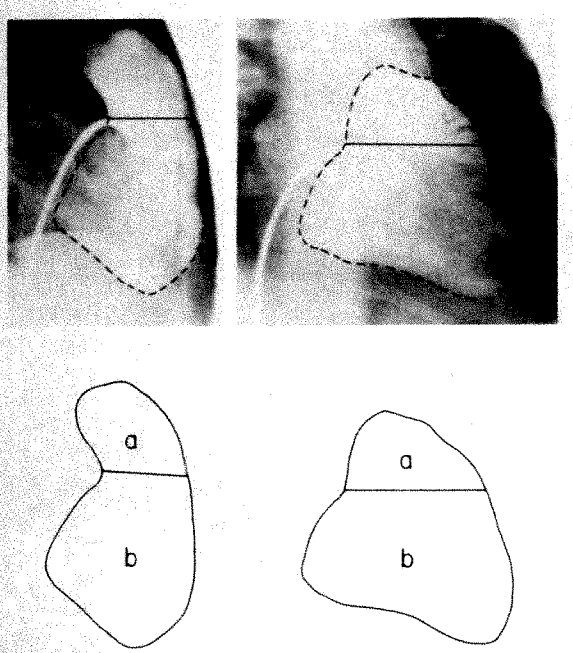

FIGURE 2. Lateral (**left**) and anteroposterior (**right**) cineangiocardiograms of the right ventricle. The **solid line** divides the right ventricle into RV outflow (a) and RV sinus (b).

Timing of end-systole and end-diastole: There was no significant difference in end-diastolic or end-systolic area and length when these measurements were obtained using either the electrocardiogram or tricuspid valve motion to establish timing of the cardiac cycle (Table II). Furthermore, the fractional percentage of long-axis length (end-diastolic length minus end-systolic length divided by end-diastolic length) was not significantly different when values were compared using either method. Therefore, in this study we used the electrocardiogram as a reference to determine end-systolic and end-diastolic frames.

Echographic versus angiocardiographic measurements: All echographic and angiographic dimensions and area measurements were of the RV sinus. The relation between the echographic long-axis length and area to the angiographic inflow-tract length, longest length, and area measured from the biplane cineangiographic views is summarized in Table III. A good correlation existed between all paired measurements. Echographic long-axis length underestimated the longest length measured from both angiographic views at end-diastole and end-systole. The echographic long-axis length underestimated the RV inflow length measured from the anteroposterior angiographic view at both end-systole and end-diastole and slightly overestimated the angiographic inflow tract dimension in the lateral view. The echographic RV area consistently underes-

TABLE III Linear Regression Equation Between Angiographic (y) and Echocardiographic (x) Variables of the Right Ventricular Sinus

Variable (y)	Slope	Intercept	r
1. RV inflow tract length (AP)			
End-diastole	1.72	−2.19	0.82
End-systole	1.92	−2.07	0.80
RV inflow tract length (LAT)			
End-diastole	0.93	−0.34	0.88
End-systole	0.96	−0.28	0.84
2. Longest length of RVS (AP)			
End-diastole	1.60	−1.10	0.84
End-systole	1.85	−1.46	0.80
Longest length of RVS (LAT)			
End-diastole	1.37	−1.50	0.89
End-systole	1.35	−0.90	0.86
3. Area of RVS (AP)			
End-diastole	2.94	−5.65	0.86
End-systole	3.03	−3.45	0.79
Area of RVS (LAT)			
End-diastole	1.57	−0.32	0.92
End-systole	1.64	−0.82	0.85

AP = anteroposterior angiogram; LAT = lateral angiogram; RVS = right ventricular sinus.

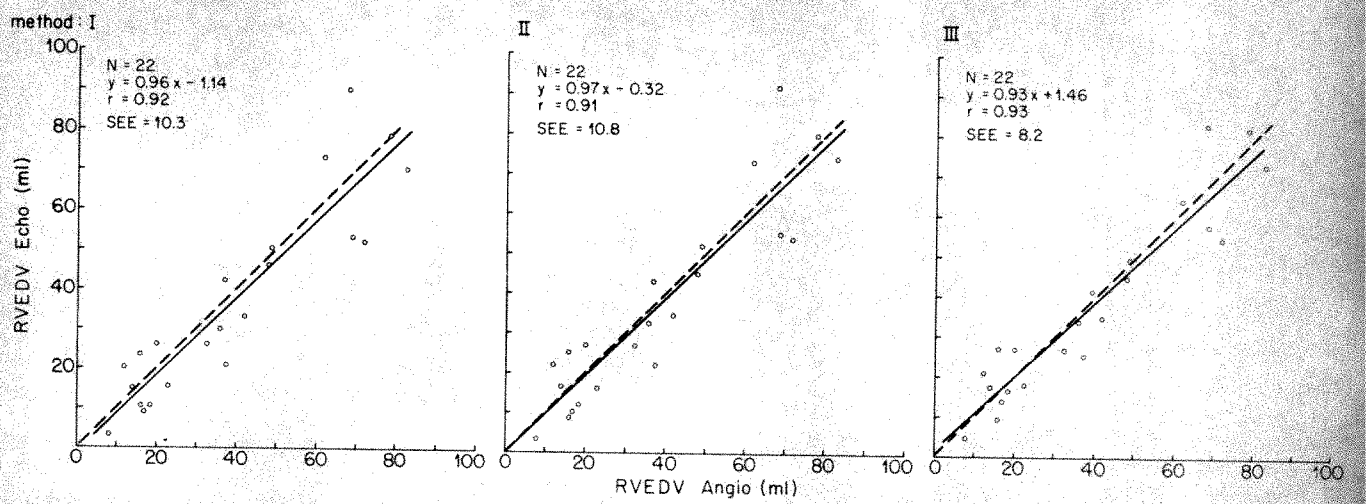

FIGURE 3. Correlation between RV end-diastolic volume calculated by echocardiography (echo) (**ordinate**) and measured by angiography (angio) (**abscissa**) for each method. r = correlation coefficient; SEE = standard error of the estimate; **dashed line** = the line of identity; **solid line** = regression line.

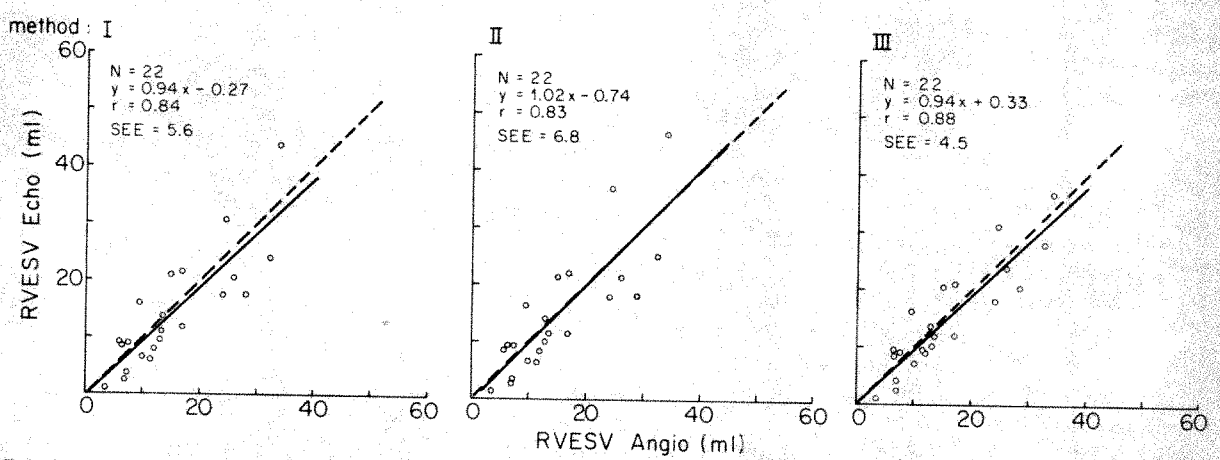

FIGURE 4. Correlation between RV end-systolic volume calculated by echocardiography (echo) and measured at angiography (angio) for each method. Format as in Figure 3.

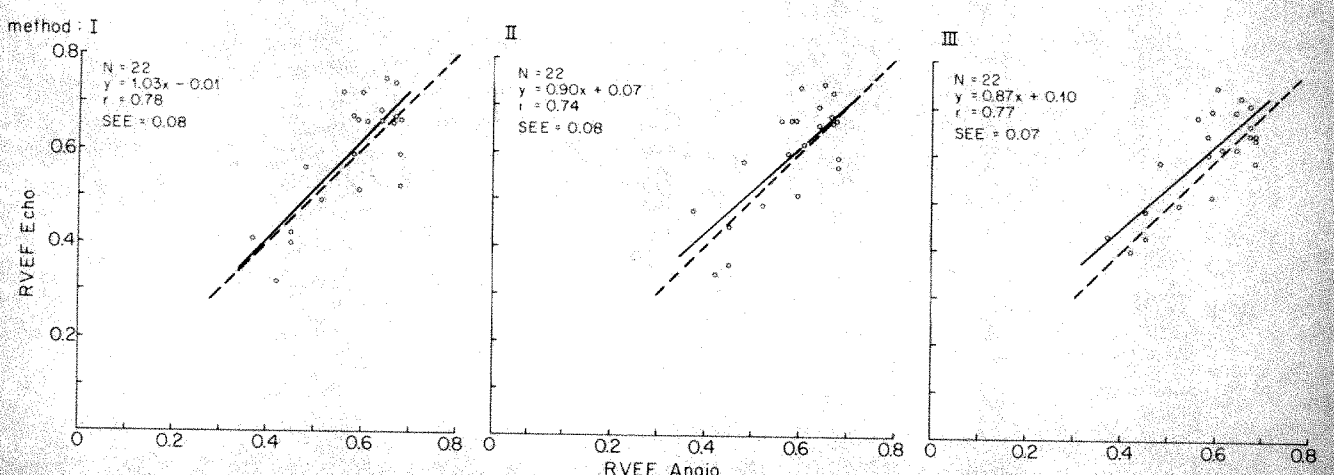

FIGURE 5. Correlation between RV ejection fraction calculated from echographic (echo) assessed volumes and calculated from angiographic (angio) volumes for each method. Format as in Figure 3.

timated areas obtained from both angiographic views. All echocardiographic measurements correlated better with lateral angiographic measurements than with anteroposterior measurements.

RV volume and ejection fraction determinations: All methods accurately estimated RV end-diastolic volume (Fig. 3). End-systolic volume correlated less favorably with angiographically determined volume (Fig. 4). The trend continued with RV ejection fraction (Fig. 5). There was no statistically significant difference between volume or ejection fraction determinations by either method.

Discussion

Two-dimensional echocardiographic imaging of the heart and great vessels has enhanced appreciably the clinician's scope of cardiac examination.[19] Various cross-sections of the right ventricle can now be visualized. Recently, 2 paired biplane methods were employed for echographic RV volume determination. Apical and subxiphoid views have been used in adults[12] and short-axis and apical views in children.[13] In the former study, however, the right ventricle was adequately viewed using these 2 planes in only 56% of adult patients. Furthermore, adequate visualization of the RV outflow tract is difficult even in children.[20] Apparently, determination of RV volume from 2-dimensional echocardiography should use the image of the RV sinus. Bommer et al[5] used the apical echographic image for measurement of RV dimensions and area and validated these variables by comparing measurements of echoed casts with actual cast data.

Validity of RV volume calculation from 2-dimensional echocardiography: To establish this validity, we compared echocardiographically determined area and length measurements from the apical 4-chamber view with angiocardiographic data. The echographic long-axis length correlated well with the angiographic RV inflow-tract length and the longest length of the RV sinus measured from either biplane cineangiographic views. However, the echographic length slightly overestimated the lateral inflow tract length and significantly underestimated all other angiographic dimensions. These results imply that the cross-section obtained from the apical 4-chamber echographic view is more comparable to the left anterior oblique angiocardiographic view, which is in agreement with Bommer's data[5] that the apical image is a right posterior oblique cross-section. The echographic area also correlated well with the angiographically determined area but routinely underestimated the angiographic area. The reasons for echographic underestimation of angiographic dimensions and area are (1) the echographic plane of sector is not identical to either angiographic plane, and (2) the echocardiogram excludes RV trabeculation. These findings indicate that the echographic area and long-axis dimension should be corrected before proceeding with volume determinations.

We have shown that total RV volume can be calculated from RV sinus volume in patients with various forms of congenital heart disease[14] (see Appendix). In the present study, therefore, total RV volume was calculated from 2-dimensional echocardiographic volume estimation of RV sinus from the apical 4-chamber image using 3 area-length formulas. It is not surprising that RV volume determined from a single echographic view predicted well angiographically determined volumes regardless of the hemodynamic derangement present. Our angiographic data obtained from 84 patients demonstrate that hemodynamic status does not affect the use of an area-length method for calculating RV volumes[14] (Appendix).

Accuracy of ejection fraction determination: Two-dimensional echocardiography best predicted end-diastolic volume. A weaker correlation existed when echographically determined end-systolic volume was compared with angiographically derived end-systolic volume. This weaker correlation may be explained by (1) spatial movement of the heart producing an altered plane of sector; (2) greater relative error in measuring a smaller end-systolic area; and (3) an error in frame selection for measuring end-systolic area and length. Indeed, the definition of end-systole by echocardiography is difficult.[21,22] In the present study, however, we demonstrated that there was no difference in echographic measurement using either tricuspid valve motion or the electrocardiogram for timing the events in the cardiac cycle. Thus, the timing of end-systole may not be a major factor. Furthermore, all the foregoing factors appeared to play a small role, because the correlation coefficient and standard error of the estimate for end-systole were good.

RV ejection fraction correlated the weakest when compared with angiocardiographically determined values. These data reflect a magnification of errors made in end-diastolic and end-systolic volume determination. In our echocardiographic methodology, biplane area-length formulas appeared of equal utility. The standard error of the estimate of end-diastolic volume and end-systolic volume was somewhat lower using the lateral uniplane method. This difference can be explained by the fact that the longest length and area of the right ventricle obtained echocardiographically correlated better with the longest length and area measured from the lateral angiographic view than from the anteroposterior view. Estimation of ejection fraction by area-length method I successfully differentiated all 4 patients with an ejection fraction less than 45%. Methods II and III identified only 3 of these 4 patients and an operative procedure did not significantly influence the predictive value of echocardiography for volume and ejection fraction calculation. Thus, further evaluation may be necessary to determine the accuracy of ejection fraction estimation with each method. It is notable that this study included 3 postoperative patients.

Limitations: Our method appears to have 2 built-in limitations: endocardial dropout and parallex distortion produced by the monitor screen. In addition, it appears tedious and time-consuming. We believe that application of direct computer analysis of the echographic image will facilitate RV volume analysis. Such image

analysis capability is commercially available in the form of a light pen microprocessor or sonic digitizer interfaced with a minicomputer.

Conclusions: These data indicate the following observations in pediatric patients with congenital heart disease: (1) The long-axis length of the right ventricle measured from the apical 4 chamber echographic view correlates well with both angiocardiographically measured RV inflow-tract length and the longest length of the RV sinus. Moreover, RV echographic area tracked the area of the sinus planimetered from angiocardiographic images. The degree of correlation was better for lateral angiocardiographic images than for anteroposterior images. (2) Two-dimensional echocardiography can accurately predict RV volumes. (3) Echographic estimation of ejection fraction was adequate but not as precise as volume determination.

Acknowledgment: We express our appreciation to George Oku, CRT, Kay Graetz, RN, and Rosemary McCanny, RN, for their assistance and to Cathy Heteniak for editing and typing this manuscript.

Appendix

We performed a preliminary study to evaluate the feasibility of RV volume determination using 4 simplified area-length methods that would provide a basis for estimation of the RV volume by 2-dimensional echocardiography.[14] In this study, 84 unoperated patients were divided into 6 groups according to their hemodynamic status: normal right and left ventricular size (group 1, n = 16), RV volume overload (group 2, n = 17), RV pressure overload (group 3, n = 13), left ventricular volume overload (group 4, n = 12), left and RV volume overload (group 5, n = 12), and tetralogy of Fallot (group 6, n = 14). The RV cineangiocardiograms were separated into RV sinus and right ventricular outflow tract by drawing a horizontal line at the superior aspect of the tricuspid valve anulus (Fig. 2). Total RV volume and sinus volume were calculated by Simpson's rule. The ratio of sinus volume to total RV volume averaged 0.75 at both end-diastole and end-systole in all patients except those with tetralogy of Fallot. In the latter patients the ratio was 0.81. *The volumes of the RV sinus were calculated by the following 4 area-length methods: Biplane area-length method 1:* $SV = 0.8488\ (A_{AP} \times A_{LAT})/LL_{AP}$; *Biplane area-length method 2:* $SV = 0.8488\ (A_{AP} \times A_{LAT})/LL_{LAT}$; *Lateral uniplane area-length method:* $SV = 0.8488\ (A_{LAT}^2)/LL_{LAT}$; *Anteroposterior uniplane area-length method:* $SV = 0.8488\ [(A_{AP})^2]/LL_{AP}$, where SV = sinus volume, A = area, LL = longest length of the right ventricular sinus, AP = anteroposterior cineangiogram, and LAT = lateral cineangiogram.

Total RV volume was calculated by multiplying sinus volume by 1.23 in patients with tetralogy of Fallot and 1.33 in all other patients. Both biplane methods and the lateral uniplane method predicted accurately the total RV volume. However, biplane method 1 overestimated and the lateral uniplane method underestimated Simpson's rule RV volumes

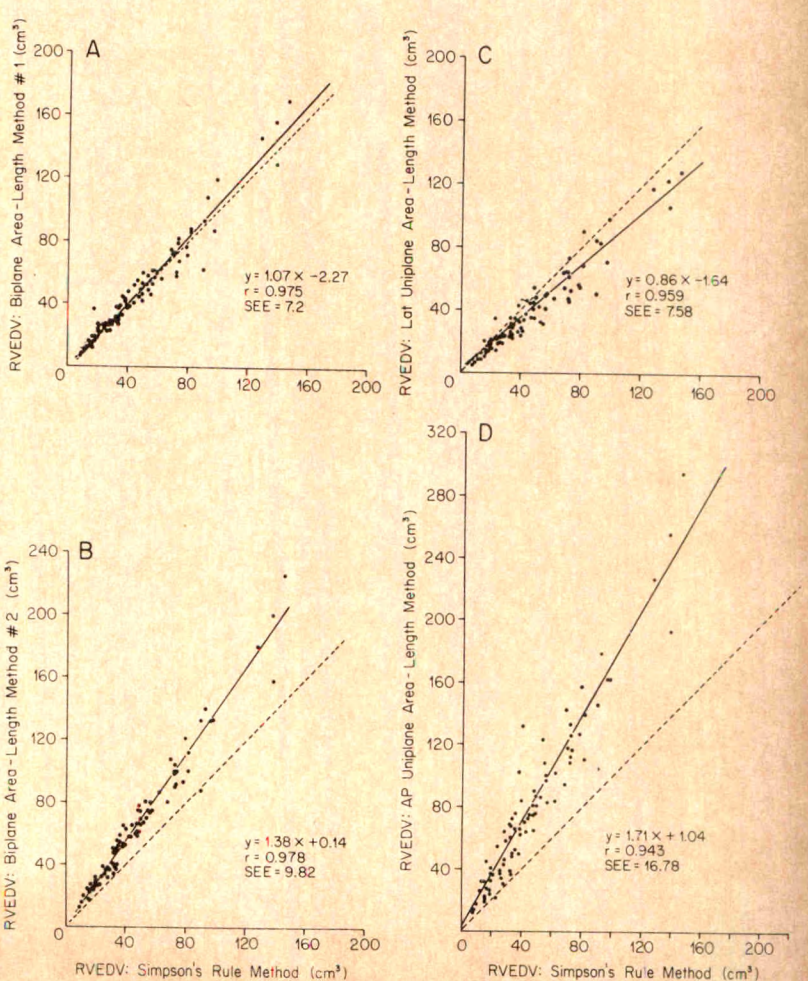

FIGURE 6. RV end-diastolic volume calculated by the 4 area-length methods as a function of RV end-diastolic volume calculated by Simpson's rule method. AP = anteroposterior.

(Fig. 6 and 7). The slope of the regression line was therefore used to correct for the degree of over- or underestimation. Thus, the following area-length formulas for calculating RV volume in patients without tetralogy of Fallot were obtained: *Biplane method 1:* $V = 1.061 \times (A_{AP} \times A_{LAT})/LL_{AP}$; *Biplane method 2:* $V = 0.849 \times (A_{AP} \times A_{LAT})/LL_{LAT}$; *Lateral uniplane method:* $V = 1.316 \times [(A_{LAT})^2]/LL_{LAT}$.

For children with tetralogy of Fallot, the constants were 0.981, 0.785, and 1.217 for biplane methods 1 and 2 and the lateral uniplane method, respectively. Moreover, RV ejection fraction was accurately predicted by these 3 methods (Fig. 8). These data indicate that these simplified methods are accurate for RV volume determination, irrespective of the patient's hemodynamic derangement.

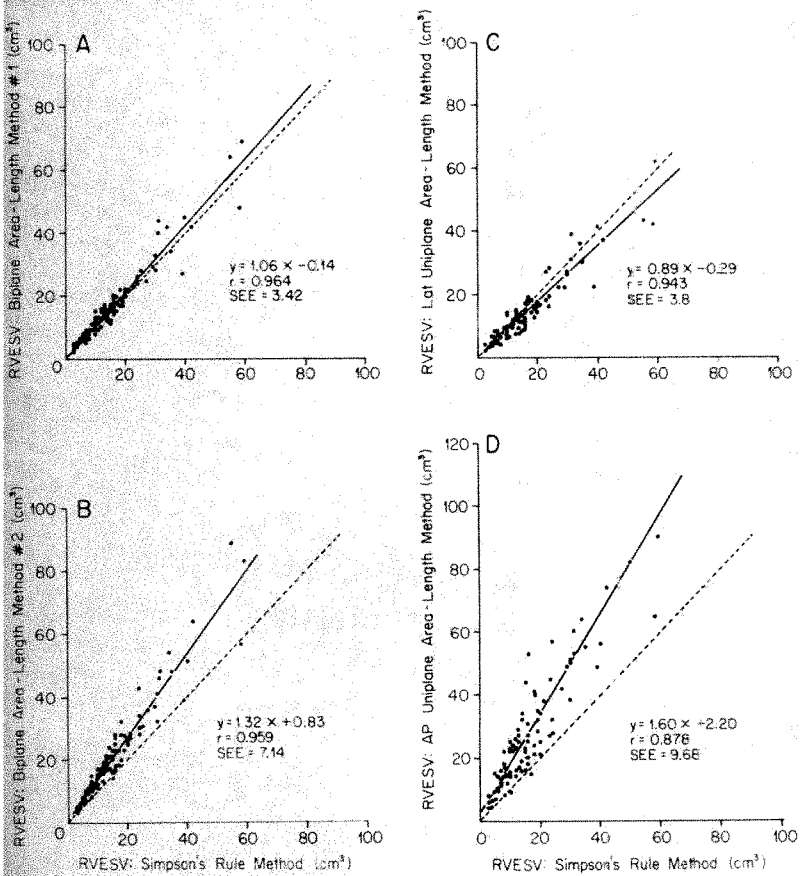

FIGURE 7. RV end-systolic volume calculated by the 4 area-length methods as a function of right ventricular end-systolic volume calculated by Simpson's rule method. LAT = lateral. Format as in Figure 6.

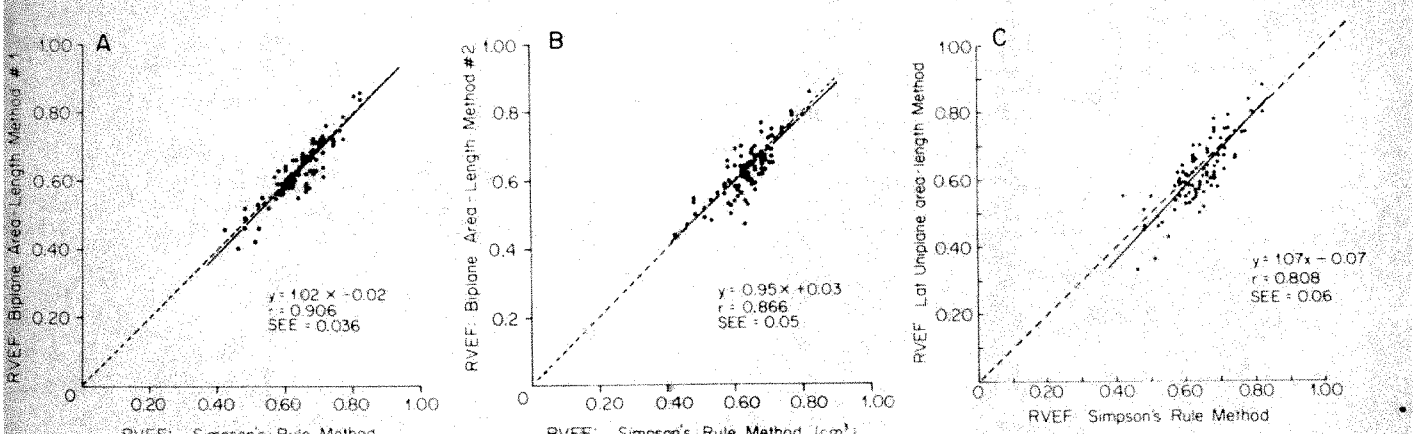

FIGURE 8. RV ejection fraction calculated by the 2 biplane area-length methods and lateral (Lat) uniplane method as a function of RV ejection fraction calculated by Simpson's rule method.

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Two-Dimensional Echocardiographic Evaluation of Persistent Truncus Arteriosus

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Using a phased-array, wide angle sector-scanner, 2-dimensional echocardiograms were obtained in 3 patients with persistent truncus arteriosus. Type I was found in 2 patients and type II in 1 patient. In the patient with type II truncal valve stenosis was also present. Using a combination of short-axis views at the cardiac base, with 30° superior transducer angulation and parasternal long-axis views, the truncus arteriosus and the pattern of pulmonary arteries were demonstrated in each case.

M-mode echocardiographic diagnosis of persistent truncus arteriosus is based on the presence of a large arterial trunk overriding the interventricular septum and the inability to image the pulmonary valve.[1] Truncal valve thickening and an enlarged left atrium may also be present. However, these features do not differentiate this anomaly from tetralogy of Fallot or from pulmonary valve atresia and ventricular septal defect. Two-dimensional echocardiography provides a method to evaluate the relation between the truncus and the interventricular septum as well as to determine the presence or absence of right ventricular outflow. Previously, identification of the origin of the pulmonary arteries from the truncus arteriosus had been possible utilizing either a subcostal,[2,3] suprasternal,[4] or long-axis view.[5] In this report we describe the 2-dimensional echocardiographic features in 3 infants studied in our institution. Using a combination of short-axis views at the cardiac base with 30° superior transducer angulation and parasternal long-axis scans, the origin of the pulmonary arteries from the truncal root was clearly identified in each case. Truncus arteriosus type I was found in 2 infants and type II in 1. The diagnosis was confirmed by cineangiocardiography and subsequently at operation in each case.

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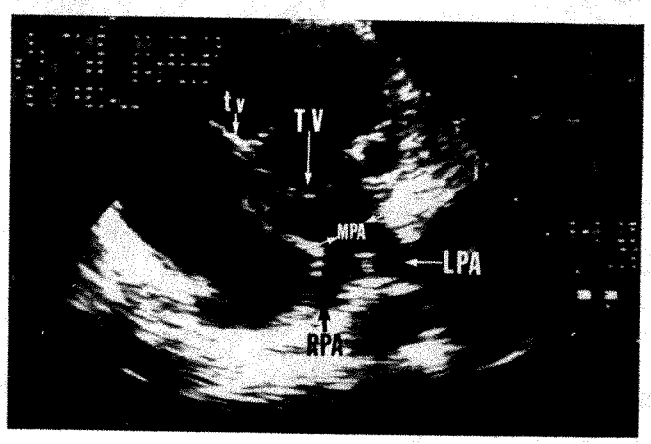
Methods

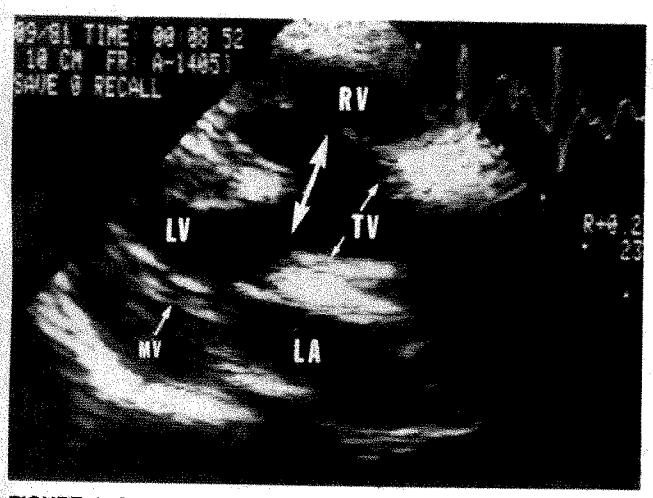
Three infants, aged 1 year, 4 weeks, and 7 months, respectively, underwent 2-dimensional echocardiographic study using a Varian V-3400R Associates 80° phased-array sector-scanner with a 3.5 MHz transducer. The image was displayed on a video monitor and recorded in real time on 0.5 inch video cassette tape. Still-frame pictures of the videotaped images were obtained for presentation. Each patient was examined in the supine and left lateral positions. Long- and short-axis, apical and subcostal 4-chamber, and subcostal long-axis scans were recorded as previously described.[6] Cross-sectional views through the truncus and pulmonary arteries using short-axis scans at the cardiac base with 30° superior transducer angulation were obtained in Cases 1 and 3, and scanning in an intermediate position between the parasternal long- and short-axis planes in Case 2.

Case Reports

Case 1. A 1 year old white girl was first seen at 8 days of age because of cyanosis and tachypnea. A 2-dimensional echocardiogram in the short-axis view showed a large truncal valve and anulus. A discrete main pulmonary artery was identified as originating from the truncus and shortly bifurcated in the right and left pulmonary arteries (Fig. 1, top). In the long-axis view a dilated great artery overriding the interventricular septum was well imaged (Fig. 1, bottom left). The diagnosis of truncus arteriosus type I was confirmed by cineangiocardiography (Fig. 1, bottom right) and subsequently at operation. The patient had a satisfactory postoperative course and is well 2 months after the operation.

Case 2. A 7 month old infant was referred with a history of respiratory distress since the newborn period. A 2-dimensional echocardiogram revealed a large arterial trunk overriding the interventricular septum in the long-axis view. Combining parasternal long- and short-axis scans, a single, large semilunar valve was imaged and with 30° superior angulation of the transducer; a main pulmonary artery was outlined, origi-





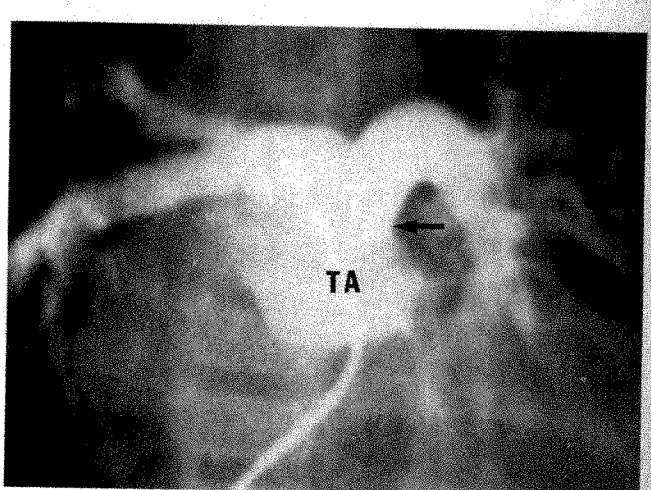


FIGURE 1. Case 1. **Top,** a 2-dimensional echocardiogram in the short axis view demonstrates persistent truncus arteriosus, type I. The truncal valve (TV) as well as the main pulmonary artery (MPA) is seen branching into the left (LPA) and right (RPA) pulmonary arteries. In addition, in this view the tricuspid valve (tv) is visualized. **Bottom left,** a 2-dimensional echocardiogram in the long axis shows a typical subtruncal ventricular septal defect (**large arrows**) and overriding of the interventricular septum by the truncal valve (TV). In this view the right ventricle (RV), left ventricle (LV), left atrium (LA), and mitral valve (MV) are also seen. **Bottom right,** contrast injection into the persistent truncus arteriosus (TA) shows a type I anomaly with a short main pulmonary artery (**arrow**) which branches into the right and left pulmonary arteries.

nating from the persistent truncus arteriosus and shortly bifurcating into the right and left branches (Fig. 2, top). Truncus arteriosus type I was confirmed by angled cineangiocardiography (Fig. 2, bottom) and subsequently at surgery. After a complicated course, the patient died in the early postoperative period.

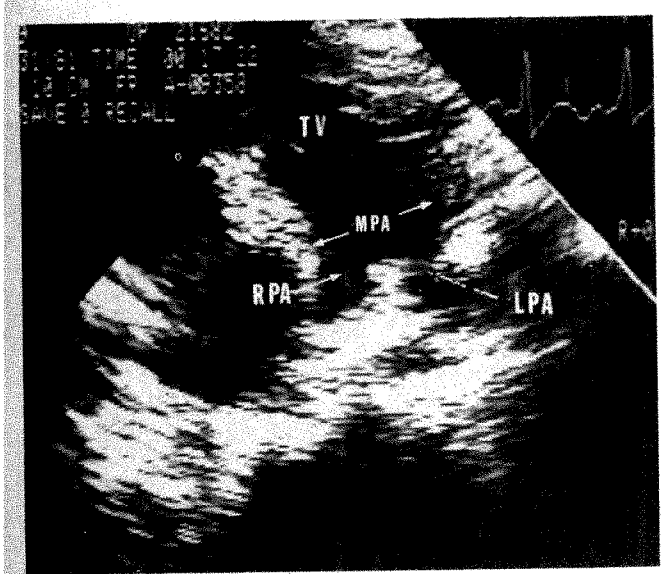
Case 3. A 6-week old infant was referred because of signs of increasing respiratory distress. A 2-dimensional echocardiogram in the short-axis view showed a dilated truncal anulus. Thick cusps were imaged and the right and left pulmonary arteries were seen originating separately from the truncus (Fig. 3, top). In the long-axis view a dilated great artery was demonstrated overriding the interventricular septum. Also in this view the semilunar cusps appeared thick and exhibited decreased motion. Angled cineangiocardiography demonstrated truncus arteriosus type II, with the right and left pulmonary arteries branching directly from the truncus (Fig. 3, bottom). Increased thickness and decreased motion of the valve with a dome configuration were also seen. At operation the diagnosis was confirmed and successful repair was accomplished.

Discussion

First reported by Buchanan[7] in 1864, persistent truncus arteriosus was classified by Collet and Edwards[8] into 4 types. In type I a discrete main pulmonary artery of variable length arises from the truncus arteriosus before bifurcating into the right and left pulmonary arteries. In type II and III there is no main pulmonary artery, and the right and left pulmonary arteries originate separately from either the lateral or the dorsal wall of the truncus. These cases are indistinctively referred to as type II. Much controversy remains as to whether type IV is truly a type of persistent truncus arteriosus or a single aortic trunk with agenesis of the sixth aortic arch.[9] Our cases are examples of type I and II.

In this study 2-dimensional echocardiography was an important method in differentiating persistent truncus arteriosus from other conotruncal anomalies in which the systemic artery overrides the interventricular septum, as in pulmonary valve atresia with ventricular

septal defect and tetralogy of Fallot. A combination of parasternal long- and short-axis scans allowed differentiation between these anomalies in each instance. Demonstration of the absence of the pulmonary valve and evaluation of the right ventricular outflow tract was possible by scanning in the short axis. In this view and with 30° superior transducer angulation, the origin of the pulmonary arteries from the truncal root was clearly demonstrated in Cases 1 and 3. Truncus arteriosus, type II, was identified in Case 3 and confirmed subsequently at cineangiocardiography and operation. In Case 2, the truncus arteriosus and pulmonary arteries were identified using an intermediate scan between parasternal long- and short-axis views with superior tranducer angulation. This finding suggests that some individual variation is possible and the echocardiographer must have this in mind when evaluating patients with truncus arteriosus.



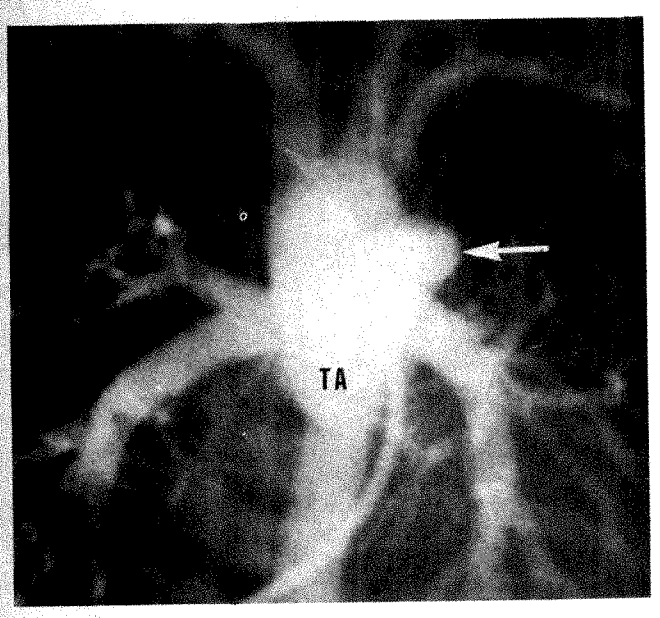
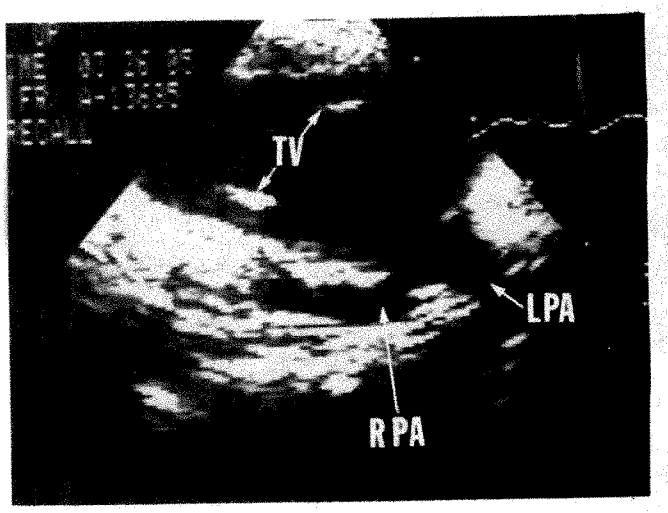


FIGURE 2. Case 2. **Top, A**, a 2-dimensional echocardiogram recorded in an intermediate position between a long- and short-axis shows the persistent truncus arteriosus and truncal valve (TV). There is a discrete main pulmonary artery (MPA) with early branching of the left (LPA) and right pulmonary arteries (RPA). **Bottom,** anteroposterior cineangiocardiogram confirms a type I persistent truncus arteriosus (TA). The main pulmonary artery (**white arrow**) and branches are clearly imaged.



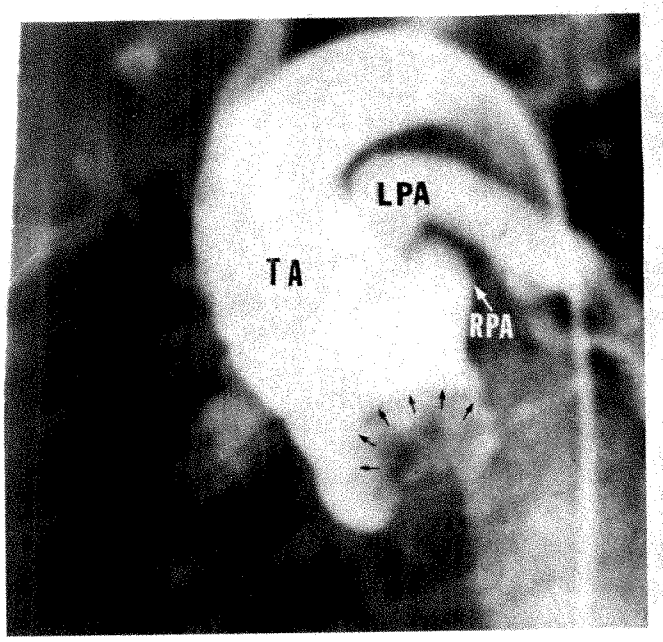


FIGURE 3. Case 3. **Top,** a 2-dimensional echocardiogram in the short axis view shows a thickened, echo-dense truncal valve (TV) and dilatation of truncal valve anulus. In addition, separate origin of the left (LPA) and right pulmonary arteries (RPA) from the truncus arteriosus is seen. **Bottom,** the 4-chamber or hepatoclavicular cineangiocardiogram demonstrates a large left-sided truncus arteriosus (TA) with separate origin of the left (LPA) and right pulmonary arteries (RPA). In addition, the truncal valve is domed (**arrows**) and stenotic.

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Two-Dimensional Echocardiographic Prospective Diagnosis Of Common Truncus Arteriosus in Infants

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With the technical assistance of SUE PAJCIC

Two-dimensional echocardiographic prospective diagnosis of truncus arteriosus was made in 7 infants. Two infants had truncus arteriosus type I, 3 patients had truncus arteriosus type II, 1 infant had truncal valve stenosis with an interrupted aortic arch, and 1 had type IV truncus arteriosus with pulmonary hypertension. Multiple imaging views were utilized to confirm the diagnosis. The parasternal long-axis view demonstrated the great vessel-ventricular septal override and the origin of the pulmonary arteries from the posterior aspect of the ascending truncus. The suprasternal notch image facilitated identification of the left- or right-sided aortic arch and the origin of the pulmonary arteries from the truncus. Transverse imaging sections at the base of the heart facilitated identification of the pulmonary artery origin of truncus arteriosus type I. Subcostal coronal and sagittal views imaged the common truncus and the ventricular septal defect.

These echocardiographic images were contrasted with and discriminated from those of an infant with aorticopulmonary window with intact ventricular septum. Although cardiac catheterization and angiography may be required to assess pulmonary arterial pressure, pulmonary vascular resistance, and the distal pulmonary arterial anatomy in truncus arteriosus, 2-dimensional echocardiography can be used to correctly establish the morphologic diagnosis of truncus arteriosus in infants.

Two-dimensional echocardiography has greatly enhanced the clinician's ability to recognize and differentiate various conotruncal abnormalities with the common feature of systemic arterial-ventricular septal override. The spatial relation of the great arteries, their concordance to the ventricular chambers, and hypoplasia or atresia of the pulmonary valve can each be assessed.[1–4] The diagnosis of truncus arteriosus is established with demonstration of (1) a solitary great artery emerging from the ventricular chambers (almost invariably associated with a ventricular septal defect), and (2) the origination of both the aorta and the pulmonary artery (or arteries) from this great artery. Further subclassification depends on where the pulmonary artery (or arteries) originate from the truncus and whether the aortic arch is interrupted.[5,6]

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We report herein observations on 7 consecutively encountered infants in whom the prospective diagnosis of truncus arteriosus was made by 2-dimensional echocardiography and subsequently confirmed by angiography and surgery. The purpose of this report is to characterize the distinctive 2-dimensional echocardiographic features of truncus arteriosus, especially with regard to the origin of the pulmonary arteries, and to compare and contrast these echocardiographic observations with those from an infant with aorticopulmonary window with an intact ventricular septum.

Methods and Patients (Table I)

All patients had 2-dimensional echocardiographic examinations utilizing an Advanced Technology Laboratory 2-dimensional sector scanner with a 5.0 MHz transducer. Most of the images were obtained in standard echocardiographic planes and displayed according to accepted standards.[7] Minor angular or positional variations from standard imaging positions are elaborated under Results.

All patients except Case 8 underwent cardiac catheterization and angiography. This infant with an aorticopulmonary window had multiple congenital anomalies; the diagnosis was confirmed at autopsy. Two infants (Cases 1 and 6) were considered to have DiGeorge's syndrome.

TABLE 1 Clinical Summary

	Echocardiography		Cardiac Catheterization				Surgery			
Patient	Diagnosis	AO Arch	Age (yr)	Weight (kg)	Diagnosis	AO Arch	Age (yr)	Weight (kg)	Procedure	Findings
1	TRN I	R	0.10	2.5	TRN II	R	0.15	2.6	PAB	TRN II
2	TRN I	L	0.10	3.7	TRN I	L	0.17	3.8	Repair	TRN I
3	TRN I	L	0.01	3.0	TRN II	L	0.04	3.0	PAB	TRN II
4	TRN IV RPA stenosis	L	2.3	8.7	TRN IV	L	2.3	8.7	Repair	TRN IV, separate RPA and LPA
5	TRN I	R	0.25	3.5	TRN I	R	0.5	4.9	Repair	TRN I
6	TRN I	R	0.10	3.1	TRN II	R	0.1	3.1	PAB	TRN II
7	TRN with TS	IAA	0.005	2.4	TRN with TS; IAA			Died before surgery		No autopsy
8	A-P window	L	None					Died at 0.25 yr		Autopsy A-P window

AO = aortic; A-P = aorticopulmonary; IAA = interrupted aortic arch; L = left; LPA = left pulmonary artery; PAB = pulmonary arterial banding; R = right; RPA = right pulmonary artery; TRN = truncus arteriosus; TS = truncal stenosis.

Results

Parasternal long-axis view: This view allowed visualization of the size and extent of the ventricular septal defect as well as the systemic arterial override in all patients except Case 8. The specific diagnosis of truncus arteriosus was suspected by the appearance of a defect in the posterior wall of the truncus, establishing communication between the truncus and the pulmonary arteries (Fig. 1). Frequently this could be appreciated by placement of the transducer in a high parasternal position (second or third left interspace) with slight rotation of the imaging plane in a clockwise or counterclockwise direction, allowing optimal imaging of the communication between the truncus and the pulmonary artery.

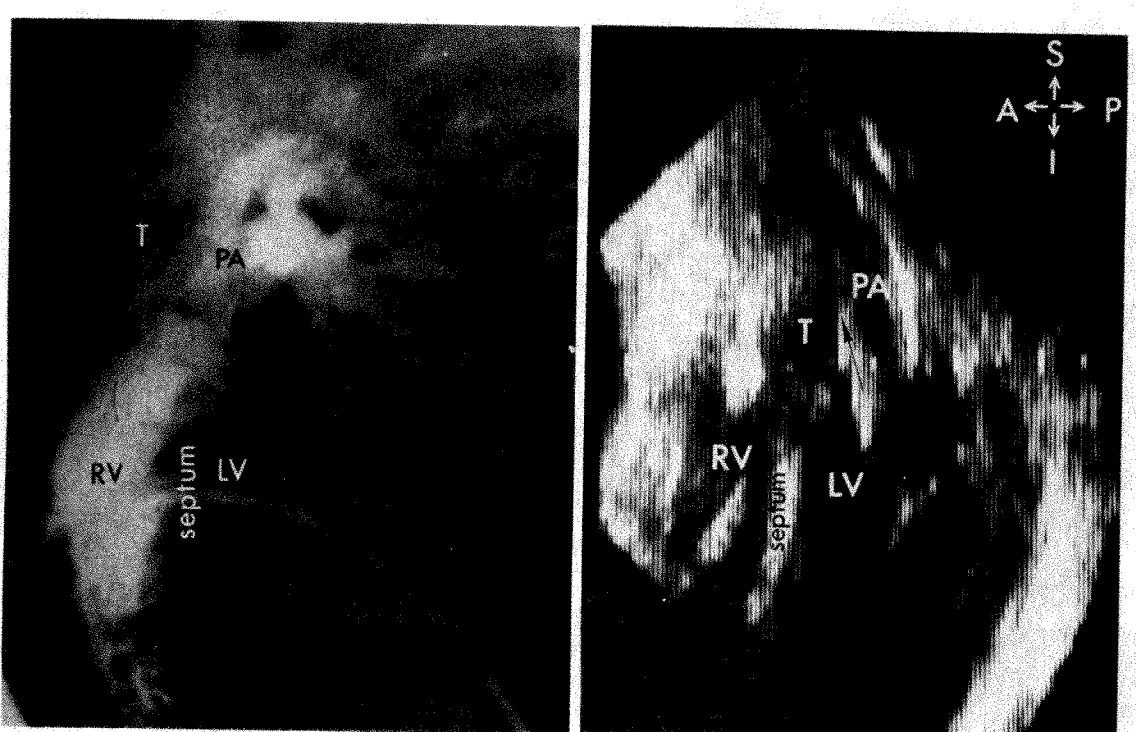

FIGURE 1. Left, angiocardiogram (Case 2) represents a right ventricular injection with opacification of the truncus arteriosus, pulmonary arteries, ascending aorta, and subsequently (through a ventricular septal defect) the left ventricle. The echocardiographic, angiographic, and surgical diagnosis was truncus, type I. **Right,** parasternal long-axis view (Case 2) demonstrates the overriding truncus arteriosus, ventricular septal defect, and the communication (**arrow**) between the truncus and the pulmonary artery. The echo image axis is realigned to correspond to the normal angiographic orientation. A = anterior; I = inferior; LV = left ventricle; P = posterior; PA = pulmonary artery; RV = right ventricle; Septum = interventricular septum; S = superior; T = common truncus arteriosus.

Parasternal transverse (short-axis) view: Successive transverse sections beginning at the cardiac base and moving superiorly to image the great arteries emerging from the heart were useful in confirming the diagnosis of truncus arteriosus (Fig. 2). The usual septation of the aorta from the pulmonary artery was incomplete, and in this view a communication between the aorta and pulmonary arteries was visualized in the 5 patients with type I or type II truncus arteriosus. In all 5 cases, an echocardiographic diagnosis of type I truncus arteriosus was suggested because a short segment of main pulmonary artery was visualized. In 3 of these cases, however, the angiographic and surgical diagnosis was type II, implying closely adjacent right and left pulmonary arteries without an intervening main pulmonary artery segment. In the infant with truncus arteriosus and interrupted aortic arch, this short-axis view clearly imaged the communication between a small ascending aorta and a very large main pulmonary artery; however, this view did not provide satisfactory visualization of the aorticopulmonary window in our solitary case.

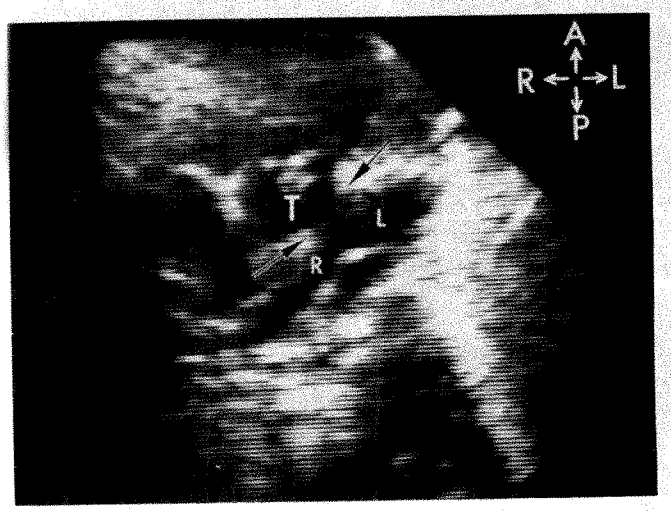

FIGURE 2. Transverse short-axis view of the truncus arteriosus (Case 2) and its communication with the pulmonary arteries (**arrows**) in a patient with type I truncus. A = anterior; L = left pulmonary artery; P = posterior; R = right pulmonary artery; T = truncus arteriosus.

Subcostal views: The subcostal approach in a coronal plane visualized the ventricular septal defect and the overriding great vessel (Fig. 3). However, the demonstration of the truncal origin of the pulmonary arteries was not possible in this plane, since the pulmonary arteries were posterior to the plane of the ventricular septal defect and ascending truncus. With angulation of the transducer into a sagittal plane, the ascending truncus, aortic arch, and descending aorta could be visualized along their long axis. In this plane, the origin of the pulmonary arteries from the posterior aspect of the ascending truncus could be demonstrated in patients with type I or II (Fig. 4). The subcostal approach imaged the intact ventricular septum in our patient with an aorticopulmonary window.

Suprasternal notch view: Using this view, the situs of the aortic arch was correctly identified as right in 3 patients, left in 4 patients, and interrupted in the remaining case. In the infant with truncus arteriosus type IV, the right pulmonary artery was identified as originating from the descending aorta. Moderate proximal right pulmonary arterial stenosis was present on 2-dimensional echocardiography (Fig. 5, left) and was

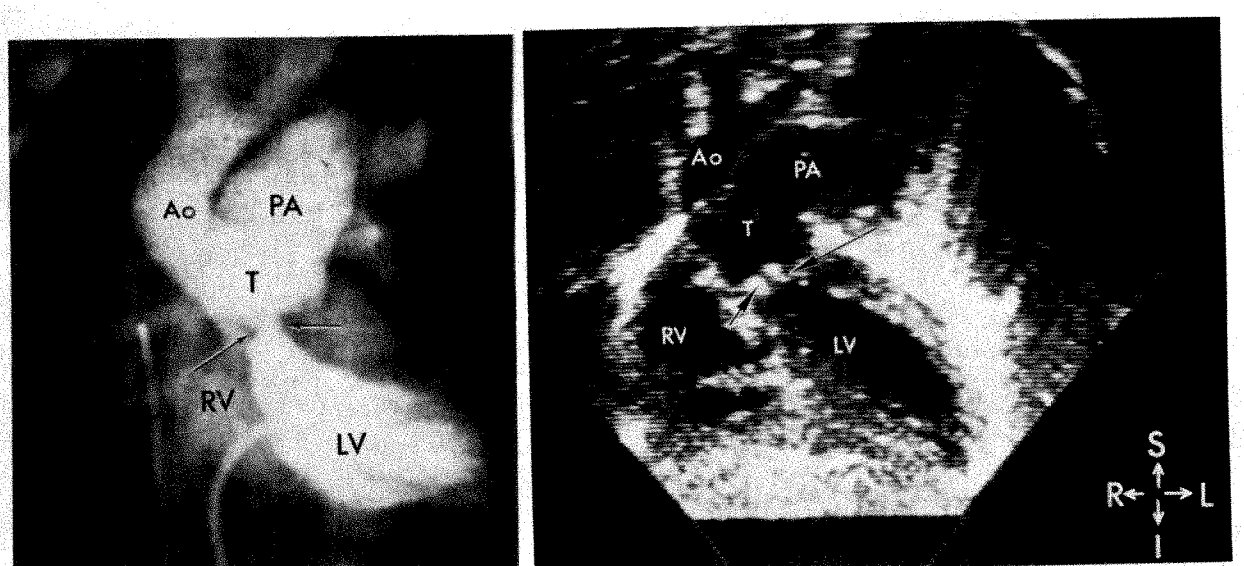

FIGURE 3. Left, angiocardiogram (Case 7) representing a left ventricular injection. The stenotic truncal valve is highlighted with **arrows** and the common truncus (T) gives rise to an interrupted aortic arch and a large pulmonary artery. The ventricular septal defect is not well visualized in this frame, although the right ventricle is opacified. **Right,** subcostal long-axis left ventricular echocardiogram obtained in coronal plane (Case 7) and inverted to correspond with angiocardiogram alignment in Figure 3A. The truncal stenosis (**arrow**) is clearly demonstrated; the ventricular septal defect and the truncus arteriosus with interrupted aortic arch are also imaged. Abbreviations as before.

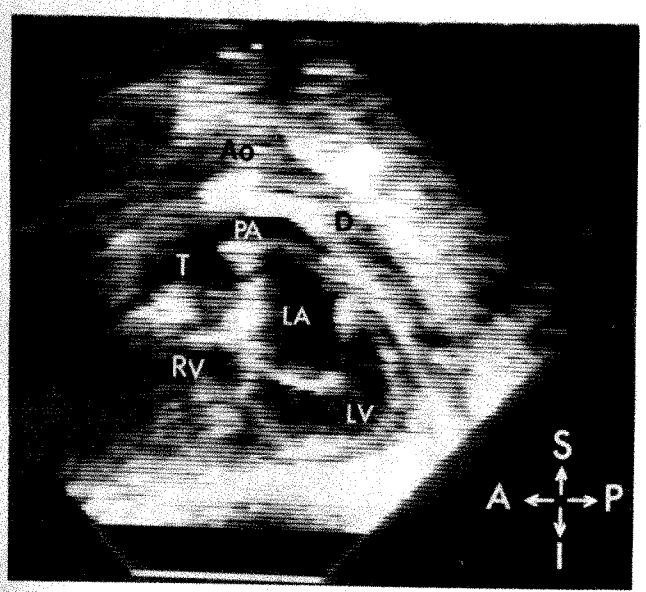

FIGURE 4. Subcostal echocardiogram, obtained in a sagittal plane (Case 3) and inverted to conventional head-foot axis, visualizes the truncus arteriosus, pulmonary artery, and descending aorta. In this plane, the ventricular septal defect is not imaged, but the origin of the pulmonary artery from the truncus is clear. D = descending aorta; LA = left atrium; other abbreviations as before.

confirmed anatomically at cardiac angiography (Fig. 5, right) and by pressure data. The left pulmonary artery could not be imaged on the echocardiogram but was seen on angiography and at surgery to originate more distally from the descending aorta. The suprasternal notch view imaged the aorticopulmonary window present in Case 8 (Fig. 6).

Discussion

Two-dimensional echocardiography can provide reliable identification and classification of conotruncal abnormalities. Although previous studies have described some of the echocardiographic findings in patients with truncus arteriosus,[1–3,8] our study, based on the prospective echocardiographic diagnosis of truncus arteriosus in 7 infants, extends those observations using multiple imaging planes.

The parasternal long-axis view demonstrates the systemic arterial override and the ventricular septal defect in patients with truncus arteriosus. This nonspecific finding also occurs in tetralogy of Fallot, pulmonary atresia with a ventricular septal defect, isolated large subaortic ventricular septal defect, double outlet right ventricle, and, occasionally, in complete transposition of the great arteries with a ventricular septal defect. The specific diagnosis of truncus arteriosus may be considered if in this view a communication can be demonstrated between the pulmonary artery and the truncus arteriosus.

Short-axis scans at the base of the heart identify hypoplasia of the right ventricular outflow tract in tetralogy of Fallot and ventricular-arterial discordance in transposition of the great arteries. Thus, tetralogy of Fallot, transposition of the great arteries, and double outlet right ventricle can be differentiated both from normal and from each other.[1,8] Careful scanning at the base of the heart facilitates the diagnosis of truncus arteriosus, since the solitary semilunar valve and origin of the pulmonary arteries from the truncus can be visualized.

Subcostal views are particularly useful in small infants since in a single view, extensive intracardiac

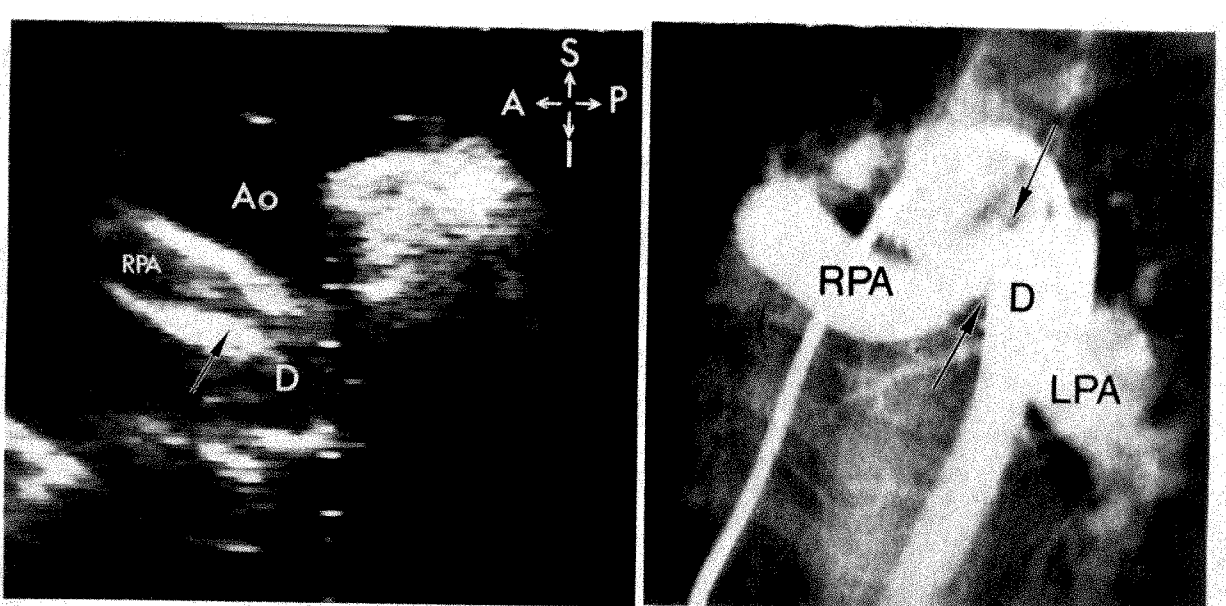

FIGURE 5. Left, angiogram (Case 4, type IV truncus arteriosus). Injection into the descending aorta (D) demonstrates (**arrows**) mild stenosis of the proximal right pulmonary artery (RPA), which is large in caliber. The left pulmonary artery originates from a more distal position on the descending aorta. **Right,** suprasternal notch echocardiogram (Case 8) clearly imaging the transverse aorta, descending aorta, and right pulmonary artery with proximal stenosis. LPA = left pulmonary artery; other abbreviations as before.

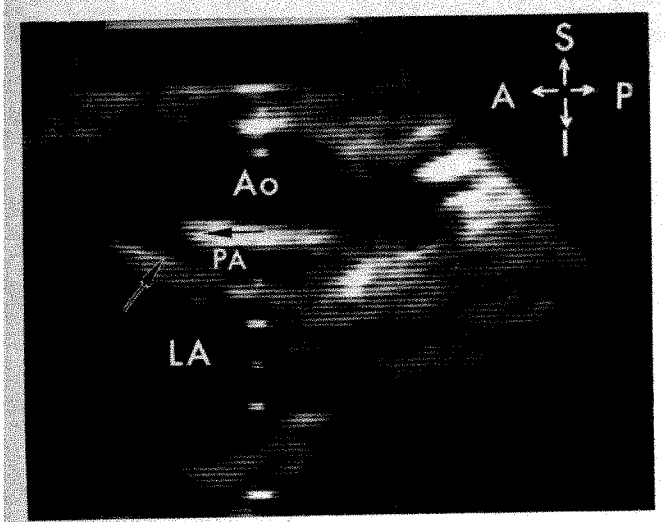

FIGURE 6. Suprasternal notch view of ascending aorta and aorticopulmonary window in Patient 8. **Arrows** indicate the extent of the aorticopulmonary window. Ao = aortic arch; other abbreviations as before.

structures and extracardiac vessels and their connections can be imaged. The early bifurcation of the pulmonary artery can be used to identify this structure as it emerges from the left ventricle in patients with complete transposition.[9] Similarly, the origin of both great arteries from the right ventricle can be demonstrated with this approach. The subcostal sagittal plane image allowed identification of the aortic arch and origin of the pulmonary arteries from the truncus in our patients with truncus types I or II and truncus arteriosus with interrupted aortic arch.

The suprasternal notch view reliably identifies the great arteries leaving the cardiac chambers and their mutual relationships.[10] The situs of the aortic arch was reliably identified and incomplete septation of the aortic arch was detected in our patient with an aorticopulmonary window. The right pulmonary artery can often be visualized from this approach, but the left pulmonary artery is often not seen because of ultrasound reflections by intervening lung tissue.

It is important to use multiple imaging planes to substantiate the diagnosis of truncus arteriosus. Although the distal pulmonary arteries cannot be visualized, the proximal connections with the truncus arteriosus, the ventricular septal defect, and the situs of the aortic arch can each be reliably demonstrated. Although we were able to correctly establish the diagnosis of truncus arteriosus in the 7 infants in our series, we could not distinguish type I from type II, since a short segment of intervening main pulmonary artery was suggested from echocardiographic images even in the 3 patients with type II anatomy. This differentiation can at times even be difficult angiographically but would be apparent at the time of surgery and would modify somewhat the surgical approach to pulmonary artery banding or conduit placement with primary repair. The prospective diagnosis of common truncus arteriosus can be reliably established by 2-dimensional echocardiography; if necessary, subsequent invasive studies may then be performed more expeditiously with less contrast agent and hence greater safety in infants who are critically ill.

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Two-Dimensional Echocardiographic Features of Interruption of the Aortic Arch

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The 2-dimensional echocardiographic features of interruption of the aortic arch are presented based on analysis of the echocardiograms and angiograms from 8 infants: 2 with type A and 6 with type B interruption. Each infant had a patent ductus arteriosus, 6 had a conoventricular septal defect with leftward deviation of the conal septum, 1 had truncus arteriosus with truncal valve stenosis, and 1 had a distal aortopulmonary septal defect with an intact ventricular septum. Echocardiographic images obtained from the suprasternal notch or from a high parasternal approach demonstrated the interruption of the aortic arch and continuation of the patent ductus arteriosus into the descending aorta. These findings were compared with those in infants with aortic atresia and a hypoplastic ascending aorta or discrete coarctation of the aorta with tubular hypoplasia of the aortic arch. Types A and B interruption of the aortic arch were easily differentiated and the caliber of the patent ductus arteriosus was assessed. The characteristic conoventricular septal defect was readily visualized from an apex 2-chamber view or from a subcostal sagittal plane view. With this information subsequent angiography can be more expeditiously performed in this group of critically ill infants.

Two-dimensional echocardiography provides noninvasive visualization of the great arteries emerging from the heart and their mutual relations. Atresia or stenosis of the semilunar valves can be readily detected. The situs of the aortic arch can be established and the presence of supravalvular aortic stenosis or coarctation of the aorta can be determined.[1-5]

This report characterizes the 2-dimensional echocardiographic features of interruption of the aortic arch, based on experience with 8 infants. In previous reports individual patients with interruption of the aortic arch have been described,[1-6] but our series of 8 neonates demonstrates further that the morphologic diagnosis of interruption of the aortic arch type A or B can be made by echocardiography. The presence of an associated patent ductus arteriosus or ventricular septal defect was also demonstrated by echocardiography. We compare these findings with those in (1) a neonate with aortic atresia and hypoplasia of the ascending aorta, and (2) a neonate with aortic coarctation and tubular hypoplasia of the aorta.

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Methods and Patients (Table I)

All patients underwent 2-dimensional echocardiographic examinations using an Advanced Technology Laboratory 2-dimensional sector scanner with a 5.0 MHz transducer. Most of the images were obtained in standard echocardiographic planes[7] and were displayed according to the usual angiographic orientation. Minor angular or positional variations from standard imaging positions are elaborated under Results.

In each infant, the echocardiographic examinations were completed before invasive studies. The diagnosis of aortic arch interruption was correctly made prospectively in all patients except Case 4. In this patient, early in our experience, the image of a widely patent ductus arteriosus was confused with that of an intact aortic arch (see Discussion). In retrospect, the interruption was obvious. This report includes our experience with interruption of the aortic arch over a 2-year period; the aforementioned case was the only diagnostic error.

Seven patients underwent cardiac catheterization and angiography. In Case 9, the anatomic diagnosis of aortic atresia was confirmed at postmortem examination. Three of the in-

TABLE I Patient Profile

Patient	Weight (kg)	Age (days)	Angiographic Diagnosis			Echocardiographic Diagnosis		
			IAA	VSD	ASD	IAA	VSD	ASD
1	3.0	8	A	+	−	A	+	−
2	3.5	14	A	+	−	A	+	−
3	2.7	3	B	+	+	B	+	+
4	2.2	2	B-1	+	+	B	+	+
5	2.9	6	B	+	−	B	+	−
6*	2.6	2	B	+	+	B	+	+
7†	3.1	25	B	−	+	B	−	+
8‡	2.9	4	B-1	+	−	B	+	−
9	2.8	2	Aortic atresia§			Aortic atresia		
10	3.2	3	Coarctation of aorta & tubular hypoplasia of aortic arch			Coarctation of aorta & tubular hypoplasia of aortic arch		

* Truncus arteriosus and truncal valve stenosis; † Distal aorticopulmonary window of the right pulmonary artery and ascending aorta; ‡ Aberrant right subclavian artery from the right pulmonary artery; § Diagnosis by autopsy. ASD = atrial septal defect (secundum); IAA = interruption of aortic arch; VSD = ventricular septal defect.

fants were considered to have the clinical diagnosis of DiGeorge's syndrome (Cases 3, 4, and 6) and 1 infant (Case 2) had Down's syndrome.

Results

Suprasternal notch or high parasternal view: The suprasternal notch or high parasternal view correctly established the morphologic diagnosis of interruption of the aortic arch in all 8 cases. In addition to the obvious interruption of the aortic arch, the morphology of the ascending aorta and its arterial branches was characteristic for type A and type B interruption, and each was distinctly different from the aortic arch of a normal neonate. While the normal ascending aorta (Fig. 1) exhibits a continuous curvature to the descending aorta, the patients with either type A or B interruption had an ascending aorta with a straight course to its branches. This was most striking in the patients with type B interruption in which the ascending aorta simply bifurcated into the innominate and left common carotid arteries (Fig. 2). In the patients with type A interruption, the ascending aorta exhibited slight curvature and had 3 branches (Fig. 3). Anomalous origin of the right subclavian artery from the descending aorta was not appreciated by echocardiographic imaging in Cases 4 or 8.

From this approach, discrimination of interruption of the aortic arch from aortic atresia with a diminutive ascending aorta (Fig. 4) (Case 9) or from coarctation of the aorta and tubular hypoplasia of the aortic arch (Case 10) was possible (Fig. 5).

Parasternal sagittal view: This imaging plane, frequently utilized to examine the right ventricular outflow tract, pulmonary valve, and main pulmonary artery, was useful in imaging the patent ductus arteriosus. The caliber of the patent ductus arteriosus in relation to the descending aorta could be determined and the response to infusion of prostaglandin E_1 could be assessed in 4 patients (Cases 3, 4, 7, and 8) (Fig. 6 and 7).

Apex 2-chamber view: This imaging plane allowed optimal display of the conoventricular septal defect in 6 cases.[8] The ventricular septal defect was oblique with respect to the plane of the ventricular septum and was invariably associated with leftward deviation of the conal septum and a variable degree of subaortic narrowing (Fig. 8). The ventricular septal defect could also be visualized from a subcostal sagittal approach.[9] In

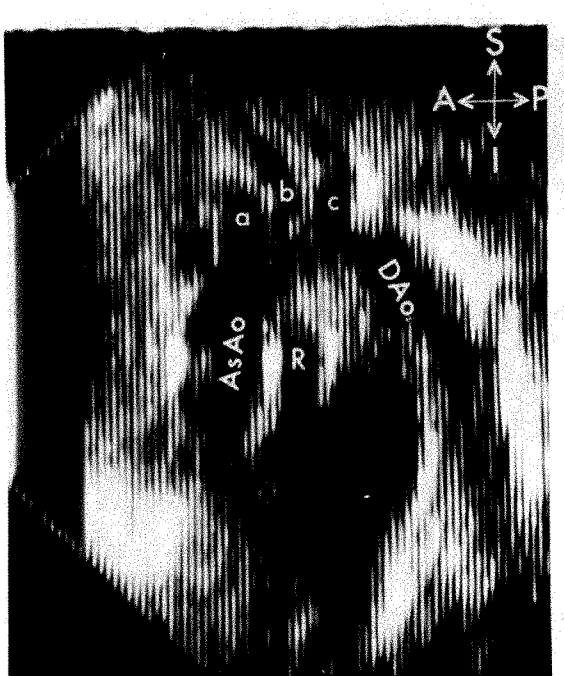


FIGURE 1. Echocardiogram obtained from a high parasternal notch approach, demonstrating a normal aortic arch with normal brachiocephalic branching. The patient has a normal heart and is 8 hours old. The echocardiogram is rotated to conform to the conventional angiographic display format. A = anterior; AsAo = ascending aorta; a = innominate artery; b = left common carotid artery; c = left subclavian artery; DAo = descending aorta; I = inferior; P = posterior; R = right pulmonary artery; S = superior.

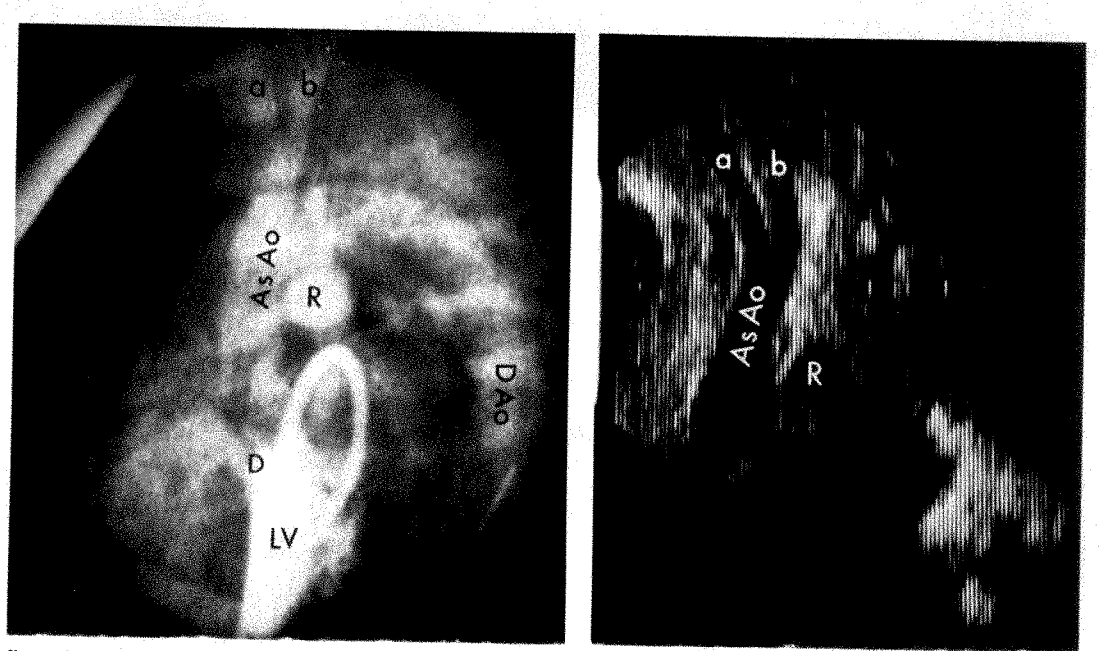


FIGURE 2. Left, angiocardiogram of left ventricle (Case 3) demonstrating interrupted aortic arch (type B) with ventricular septal defect and patent ductus arteriosus. The ascending aorta has a vertical course to its bifurcation into the innominate and the left common carotid arteries. **Right,** echocardiogram from a high parasternal position (Case 3), demonstrating bifurcation of ascending aorta into the innominate and left common carotid arteries with distal interruption of the aorta. AsAo = ascending aorta; a = innominate artery; b = left common carotid artery; D = ventricular septal defect; DAo = descending aorta; R = right pulmonary artery.

Case 7, the intact ventricular septum was correctly identified by echocardiography. Careful imaging of the ascending aorta and pulmonary arteries failed to demonstrate an aorticopulmonary septal defect which was subsequently diagnosed at cardiac catheterization.

Parasternal long-axis view: This view was not particularly useful in establishing the morphologic diagnosis of interruption of the aortic arch. Although the conoventricular septal defect was frequently appreciated in this view, the defect was better visualized from

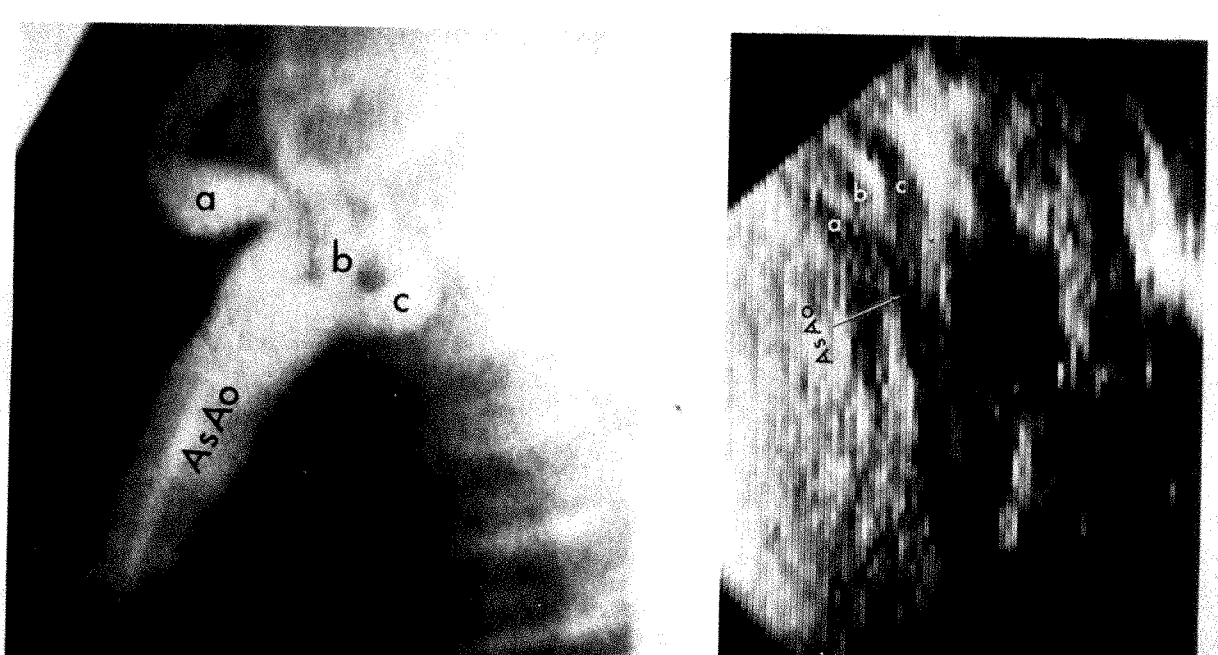


FIGURE 3. Left, selective angiogram of ascending aorta (Case 2) via the ventricular septal defect, demonstrating the interruption distal to the left subclavian artery (type A). **Right,** echocardiogram from a high parasternal approach, demonstrating 3 branches from the ascending aorta with interruption distal to the left subclavian artery (Case 2). Orientation of image as in Figure 2. AsAo = ascending aorta; a = innominate artery; b = left common carotid artery; c = left subclavian artery.

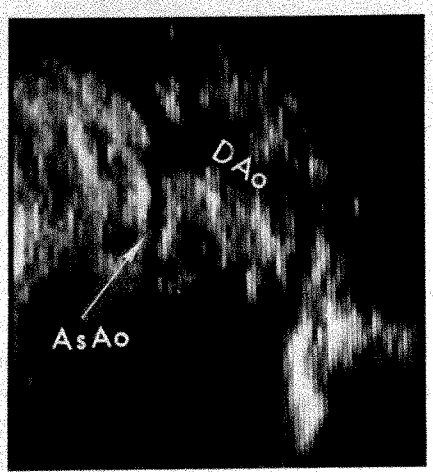


FIGURE 4. Parasternal echocardiogram obtained from a neonate with aortic atresia, confirmed at autopsy examination. The ascending aorta is very small (3 mm diameter) (Case 9). AsAo = ascending aorta; DAo = descending aorta.

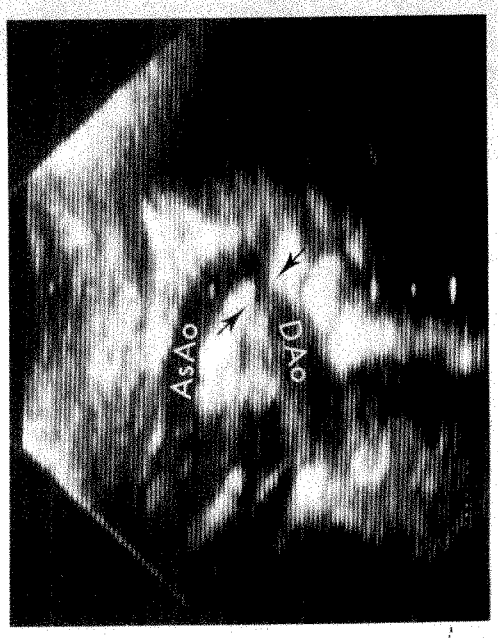
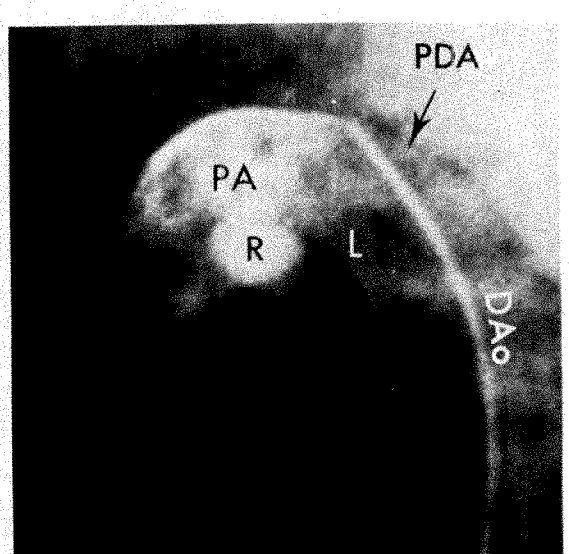


FIGURE 5. Echocardiogram obtained from the high parasternal notch approach in a neonate (Case 10) with tubular hypoplasia of the aortic arch and discrete coarctation (**arrows**). AsAo = ascending aorta; DAo = descending aorta.

a subcostal or apical approach. In our 1 patient (Case 6) with truncus arteriosus and truncal valve stenosis, this view demonstrated the valvular stenosis, the ventricular septal defect and the systemic arterial override.

Discussion

Interruption of the aortic arch, one of the most rapidly lethal forms of congenital cardiovascular disease, is amenable to surgical repair.[10–13] The symptomatic neonate with interruption of the aortic arch needs expeditious, prompt, and accurate diagnostic investigations in preparation for surgery. A distinctive conoventricular septal defect with leftward deviation of the crista supraventricularis is frequently present in patients with interruption of the aortic arch, but aorticopulmonary window, common truncus arteriosus, or other cardiovascular malformations may also be present.[10,14,15] Rarely, interruption of the aortic arch



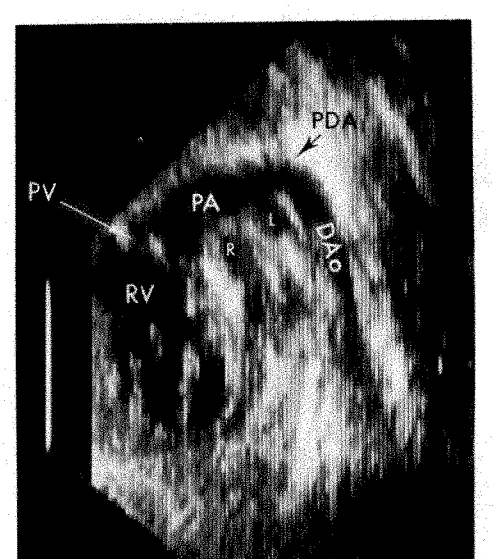


FIGURE 6. Left, lateral angiogram of injection via umbilical artery catheter into pulmonary artery. The ductus arteriosus (**arrow**) is widely patent. The patient was receiving prostaglandin E_1 to dilate the ductus arteriosus (Case 7). **Right,** Parasternal echocardiogram obtained in a sagittal plane (Case 7), demonstrating the large patent ductus arteriosus (**black arrow**) and its continuation into the descending aorta. The pulmonary valve (**white arrow**) is in the diastolic position. DAo = descending aorta; L = left pulmonary artery; PA = main pulmonary artery; PDA = patent ductus arteriosus; PV = pulmonary valve; R = right pulmonary artery; RV = right ventricle.

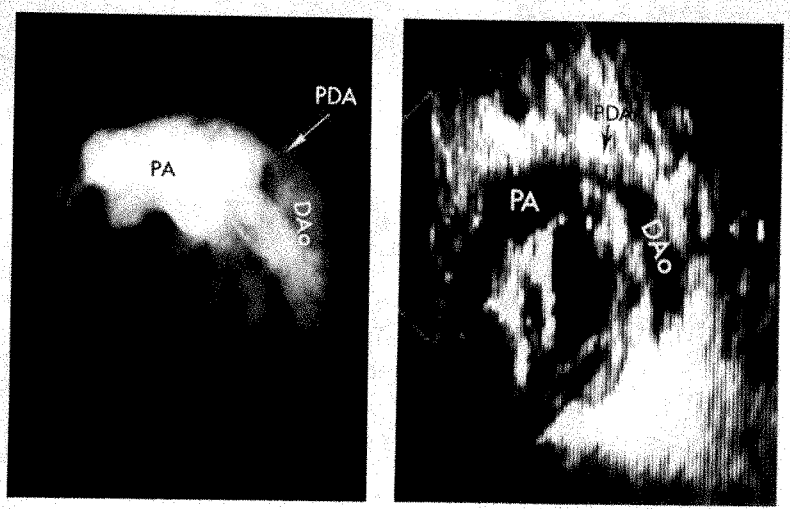


FIGURE 7. Left, lateral angiogram of pulmonary artery injection (Case 1) with demonstration of a small, restrictive patent ductus arteriosus. **Right,** parasternal echocardiogram obtained in a sagittal plane (Case 1), demonstrating the pulmonary artery, descending aorta, and closing patent ductus arteriosus. DAo = descending aorta; PA = main pulmonary artery; PDA = patent ductus arteriosus.

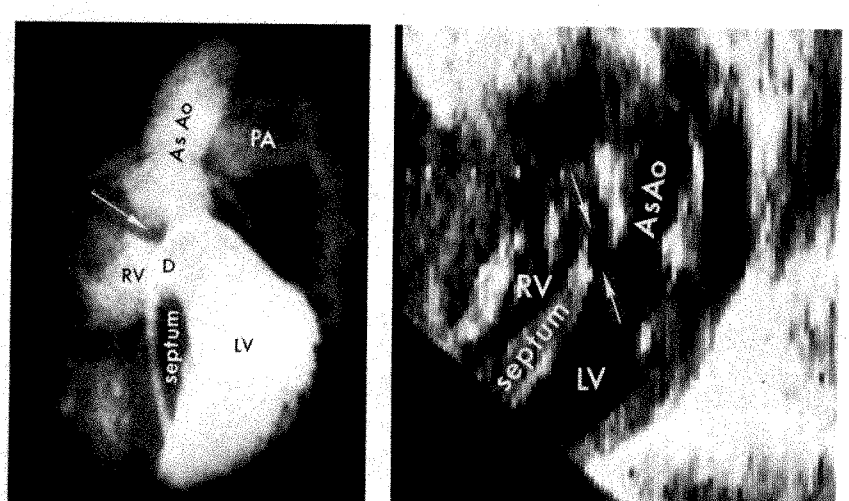


FIGURE 8. Left, Angiocardiogram of left ventricle (Case 4), showing ventricular septal defect and leftward deviation of the crista supraventricularis (**arrow**). This may result in subaortic stenosis, particularly after closure of the ventricular septal defect. **Right,** echocardiogram (apex 2-chamber views in Case 4), demonstrating the subaortic ventricular septal defect oriented obliquely (**arrows**) in the ventricular septum with leftward deviation of the crista supraventricularis. AsAo = ascending aorta; D = ventricular septal defect; LV = left ventricle; PA = pulmonary artery; RV = right ventricle; septum = interventricular septum.

is an isolated lesion. In 2 review series, only 10 of 260 patients had isolated interruption of the aortic arch and all 10 were asymptomatic during infancy.[13,16] The noninvasive evaluation of the symptomatic neonate with interruption of the aortic arch should therefore establish both the morphologic diagnosis of aortic arch interruption and the details of associated cardiac defects.

Two-dimensional echocardiography allows imaging of the aortic arch and its branches. Previous studies have established the utility of this technique in the diagnosis of coarctation of the aorta or supravalulvar aortic stenosis.[1,4] Our present study demonstrates that the morphologic diagnosis of interruption of the aortic arch can be established by echocardiography. Coarctation of the aorta, with or without tubular hypoplasia of the aortic arch and the diminutive ascending aorta of aortic atresia, can each be readily differentiated from interruption of the aortic arch. In our experience, the hypoplastic ascending aorta in aortic atresia can almost always be imaged. In interruption of the aortic arch, the frequently associated conoventricular septal defect, as well as the leftward deviation of the crista supraventricularis, could be readily visualized from the subcostal or apical approach. Certainly, the presence of an intact ventricular septum in the patient with interruption of the aortic arch should alert the echocardiographer to consider carefully other diagnoses such as proximal or

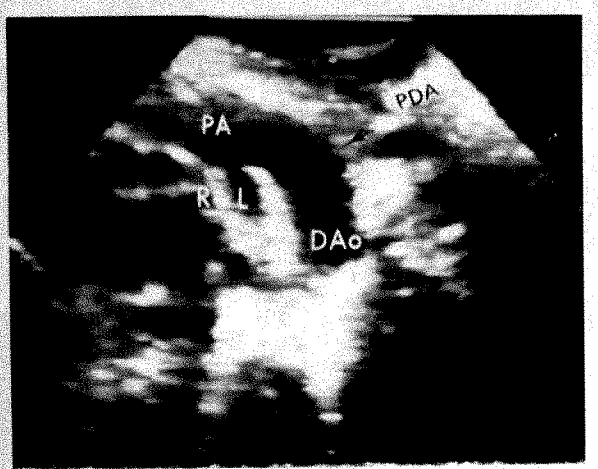


FIGURE 9. Echocardiogram obtained from suprasternal notch in a neonate with aortic atresia and a large patent ductus arteriosus (Case 9). A composite image of the pulmonary artery, patent ductus arteriosus, and descending aorta may be confused with an aortic arch. However, as seen here, the pulmonary artery branches (right and left) arise from the lesser curvature whereas the initial branches of the aorta arise from the greater curvature. DAo = descending aorta; L = left pulmonary artery; PA = main pulmonary artery; PDA = patent ductus arteriosus; R = right pulmonary artery.

distal aorticopulmonary window or anomalous origin of 1 pulmonary artery from the ascending aorta.[17]

The caliber of the patent ductus arteriosus and its response to the infusion of prostaglandin E_1 can be assessed by echocardiography, since the patent ductus arteriosus and descending aorta can easily be imaged in patients with interruption of the aortic arch. Care must be taken to differentiate an intact aortic arch from a composite image representing the main pulmonary artery, ductus arteriosus, and descending aorta structures, which can superficially mimic a normal aortic arch (Fig. 9). Careful observation of this composite image will disclose that its branches arise from the inferior aspect of this "arch" while the aortic arch gives origin to its first branches from its superior aspect. Furthermore, the origin of the main pulmonary artery can be related to the right ventricle.

Our experience indicates that 2-dimensional echocardiography can readily establish the morphologic diagnosis of interruption of the aortic arch, allow differentiation of type A from type B, and visualize the frequently associated conoventricular septal defect. In addition, the caliber of the patent ductus arteriosus can readily be assessed. Subsequent invasive studies may be more expeditiously performed in this group of critically ill infants.

Acknowledgment: We acknowledge the technical echocardiographic assistance of Sue Pajcic and the secretarial assistance of Alison Edwards.

Addendum

Since submission of this report, 2 additional patients with interruption of the aortic arch (type B) were seen and correctly recognized before angiography.

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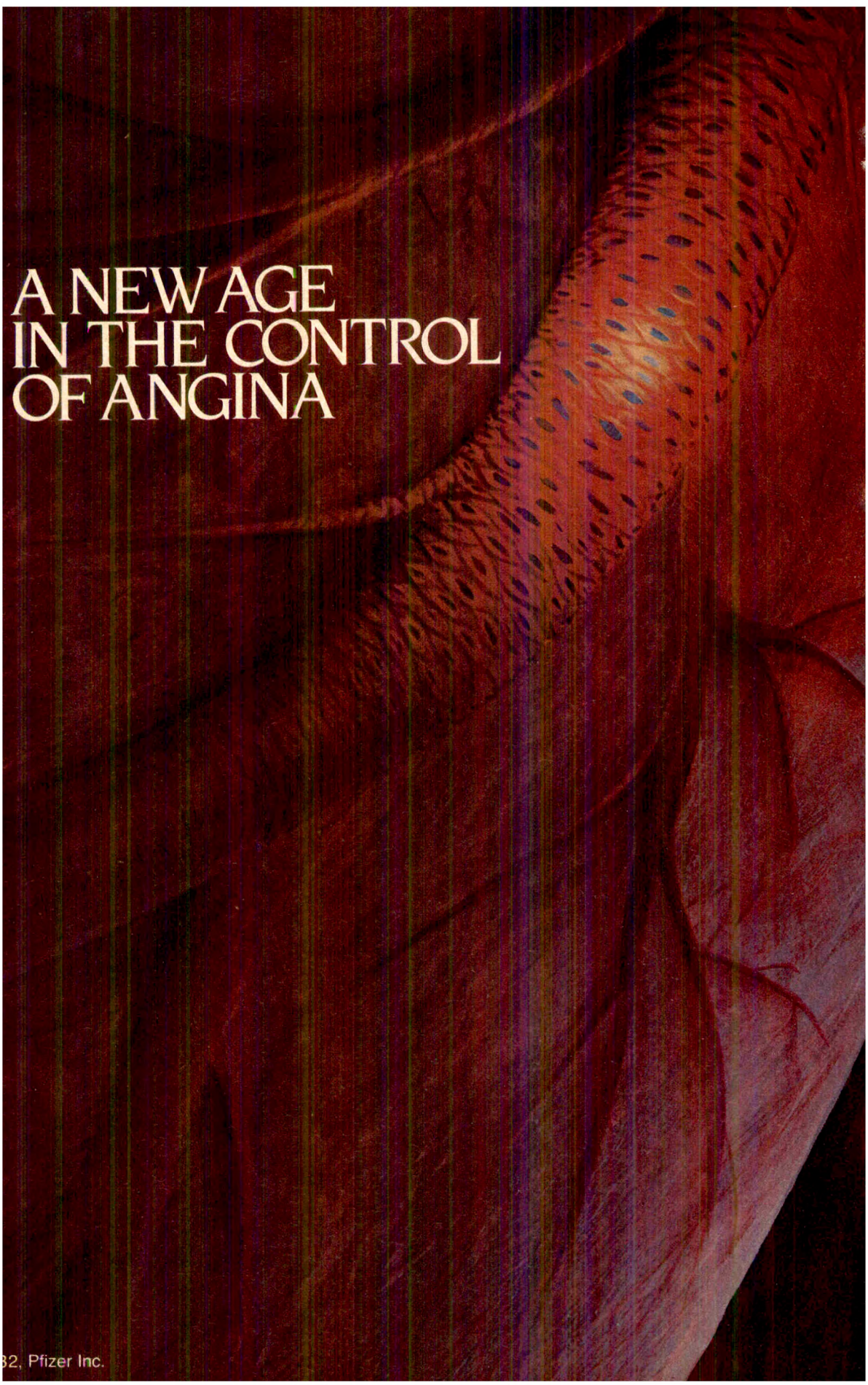
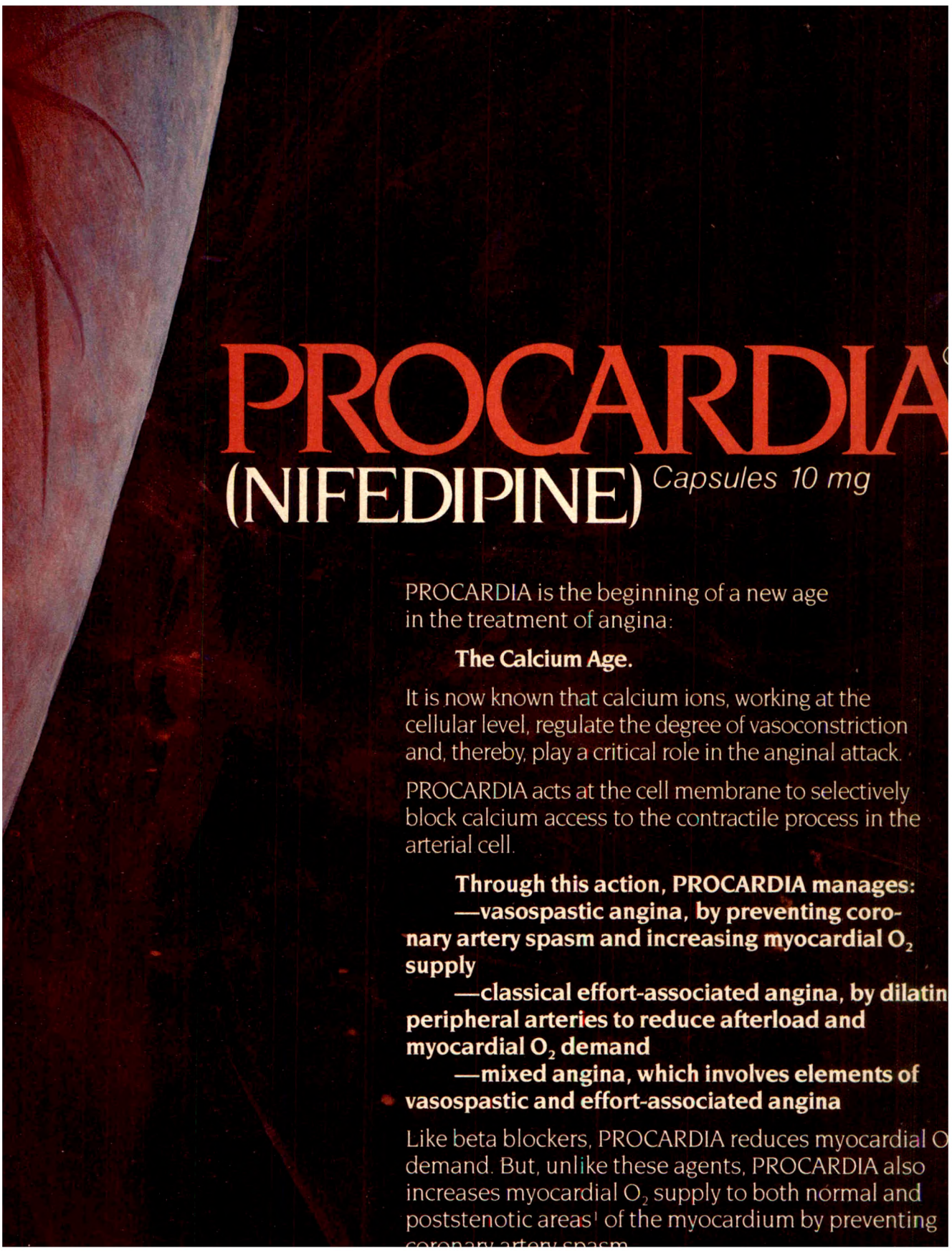
The indications for cardiac pacing are increasing as pacemakers become more sophisticated and as advanced methods for patient management become more widespread. Generally accepted indications term cardiac pacing include, but are not limited to: (1) sick sinus syndrome; (2) chronic, symptomatic drug-resistant sinus arrhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) bloc in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bund block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting such symptoms as intractable, recurrent congestive heart failure; cerebral or renal in ciency; or recurrent drug-resistant tachyarrhythmias, and who have been shown to benefit from temporary cardiac pacing, are considered candidates for permanent cardiac pacing.

The indications for permanent pacing in cases of acute myocardial infarction have not yet been rigorously defined. Factors to be considered include the location of the myocardial infarct, the presence of symptoms, ventricular rate, the mechanism of the arrhythmias, and response to therapy. In general, symptomatic drug-resistant bradyarrhythmias that impair cardiac output are considered indication pacing in patients with acute myocardial infarction, regardless of infarct location.



82, Pfizer Inc.



PROCARDIA®

(NIFEDIPINE) *Capsules 10 mg*

PROCARDIA is the beginning of a new age in the treatment of angina:

The Calcium Age.

It is now known that calcium ions, working at the cellular level, regulate the degree of vasoconstriction and, thereby, play a critical role in the anginal attack.

PROCARDIA acts at the cell membrane to selectively block calcium access to the contractile process in the arterial cell.

Through this action, PROCARDIA manages:

—vasospastic angina, by preventing coronary artery spasm and increasing myocardial O_2 supply

—classical effort-associated angina, by dilatin peripheral arteries to reduce afterload and myocardial O_2 demand

—mixed angina, which involves elements of vasospastic and effort-associated angina

Like beta blockers, PROCARDIA reduces myocardial O demand. But, unlike these agents, PROCARDIA also increases myocardial O_2 supply to both normal and poststenotic areas[1] of the myocardium by preventing coronary artery spasm.

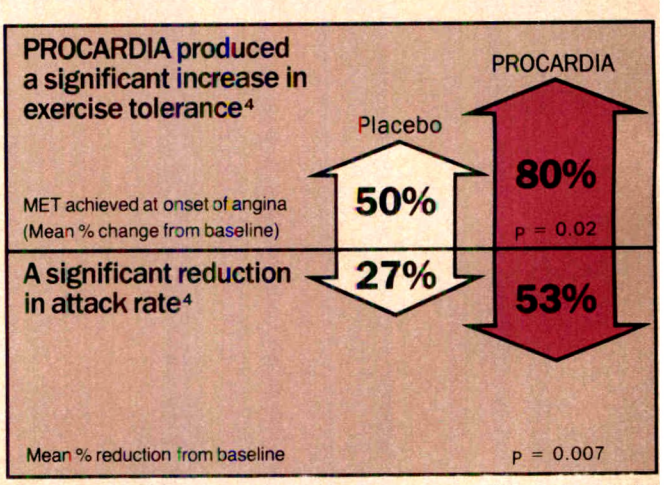
PROCARDIA
(NIFEDIPINE) *Capsules 10 mg*

PROVEN EFFECTIVE ACROSS THE SPECTRUM OF ANGINA

Contemporary medical opinion holds that the pathophysiology of angina is a spectrum ranging from pure, fixed atherosclerotic lesion to pure coronary artery spasm. Many patients, however, are believed to have a combination of both lesion and spasm.[2,3]

Angina due to pure fixed lesion can be prevented by reducing oxygen demand. Angina due to coronary artery spasm can be treated by preventing the spasm itself, thereby increasing oxygen supply. With this new understanding of angina, optimal antianginal therapy should provide this dual action: increasing O_2 supply while reducing O_2 demand.

In effort angina*
(when symptomatic despite conventional therapy)

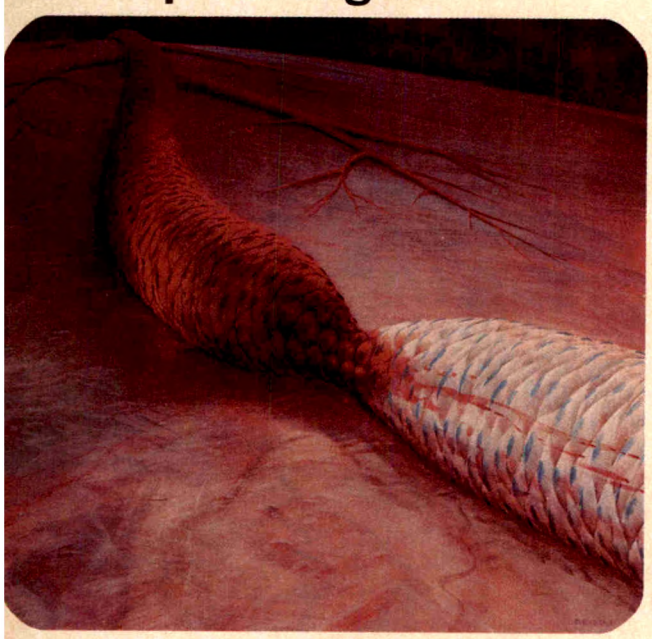


Double-blind, placebo-controlled, crossover 20-week study of 32 patients (27 evaluated for attack rate; 19 for exercise tolerance). Mean PROCARDIA dosage: 51 mg/day.

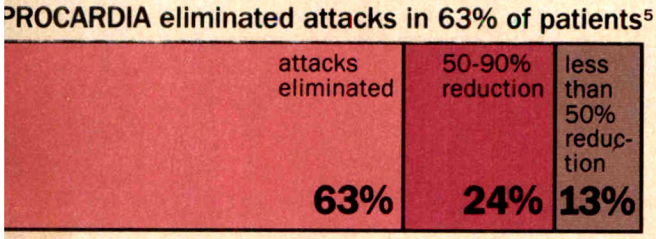
*In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Please see PROCARDIA Brief Summary on last page

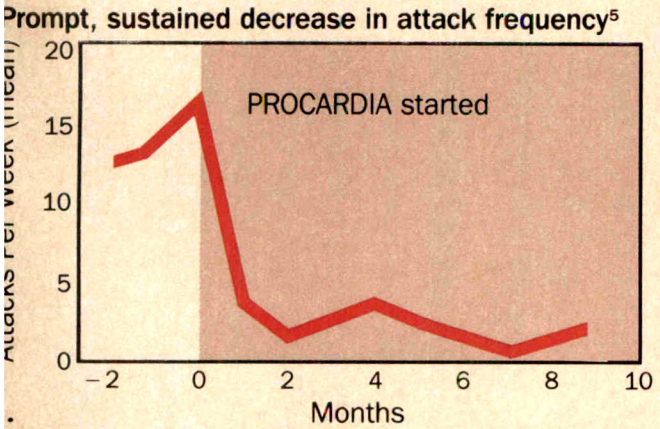
In vasospastic angina



PROCARDIA eliminated attacks in 63% of patients[5]

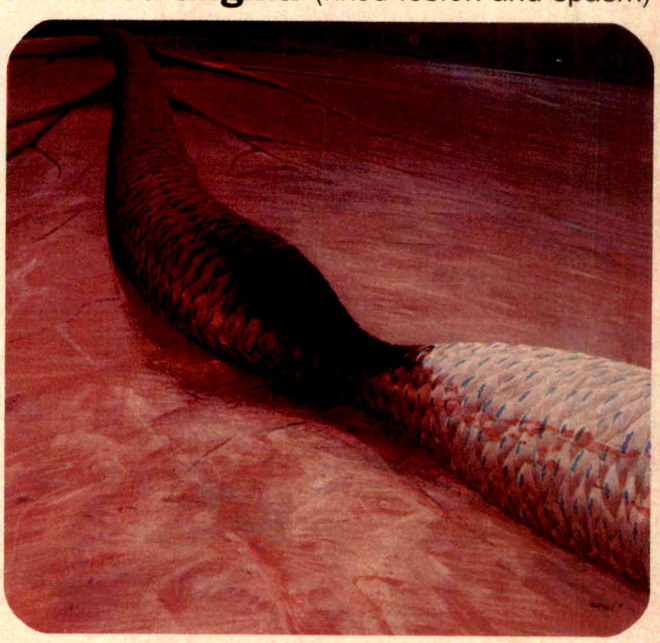


Prompt, sustained decrease in attack frequency[5]



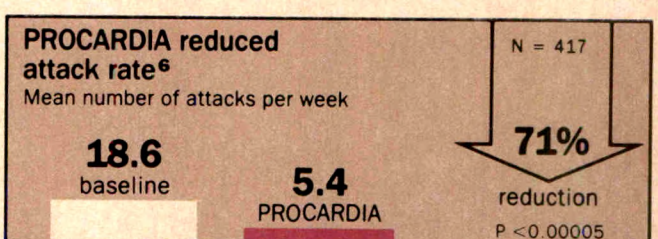
Long-term, open study of 127 patients unresponsive to beta blockers and/or nitrates with symptoms of myocardial ischemia and demonstrated coronary artery spasm. PROCARDIA dosage: 40 to 160 mg/day.

In mixed angina (fixed lesion and spasm)



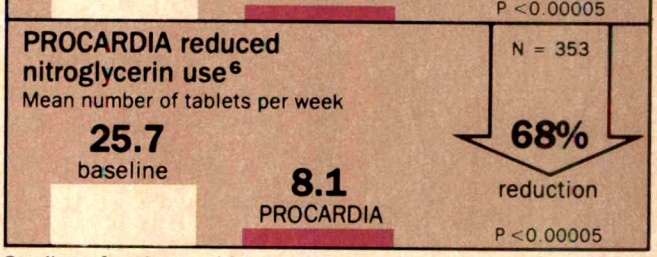
PROCARDIA reduced attack rate[6]

Mean number of attacks per week



PROCARDIA reduced nitroglycerin use[6]

Mean number of tablets per week



Studies of patients with mixed angina characterized by pain at rest and effort. Most patients (89%) were initiated on nitrate and/or beta blocker therapy but remained symptomatic. Minimum duration of nifedipine treatment two months. Nifedipine dosage: 30 to 120 mg/day.

PROCARDIA®

THE FIRST ORAL CALCIUM CHANNEL BLOCKER

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

ANGINA MANAGEMENT BEYOND BETA BLOCKERS

—Beta blockers prevent angina primarily by lowering myocardial oxygen demand. Like these agents, PROCARDIA reduces myocardial oxygen demand. However, PROCARDIA provides an added dimension of angina control by increasing myocardial oxygen supply where coronary artery spasm is present.

—Beta blockers can actually cause spasm. PROCARDIA prevents spasm.

—Beta blockers decrease myocardial perfusion in poststenotic areas. PROCARDIA increases myocardial perfusion to both normal and poststenotic areas.

—Beta-blocker treatment is limited in patients with myocardial dysfunction, COPD, asthma, bundle branch blocks, and diabetes. PROCARDIA can be given safely in all these groups of patients.

—The hypotensive effect of PROCARDIA is usually modest and well tolerated, however, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or subsequent upward dosage adjustment, and may be more likely with concomitant beta blockers.

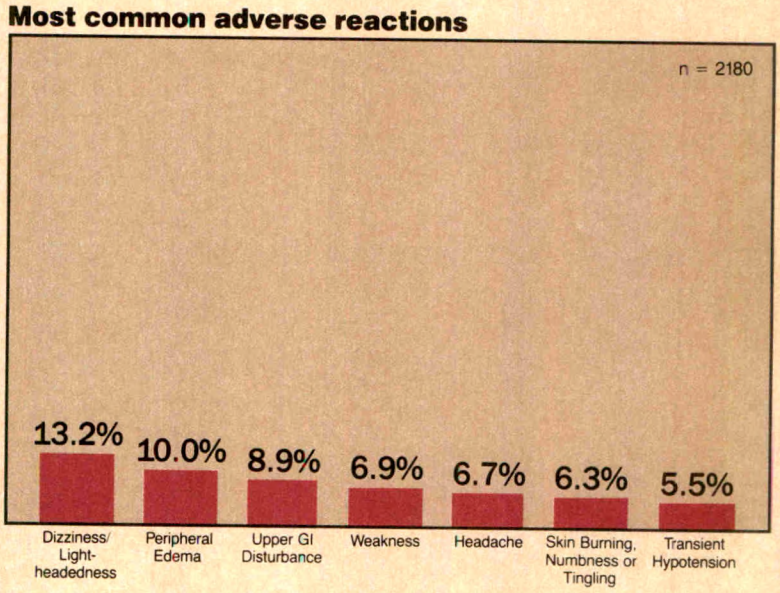
—Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA, or at the time of dosage increases. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers, if possible, rather than stopping them abruptly before beginning PROCARDIA.

—Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

THE FIRST ORAL CALCIUM CHANNEL BLOCKER...

PROVIDES PROTECTION WITH A MILD SIDE-EFFECT PROFILE

Most common adverse reactions



Information is drawn from a large uncontrolled experience in 2180 patients and presents the most frequent side effects reported with PROCARDIA.

AN ADDED ADVANTAGE: COMPATIBILITY

—MAY BE USED WITH A WIDE VARIETY OF OTHER AGENTS

—CAN BE USED WITH NITRATES AND BETA BLOCKERS WITH CAUTION (See Warnings and Precautions)

THE FIRST ORAL CALCIUM CHANNEL BLOCKER FOR THE MANAGEMENT OF ANGINA

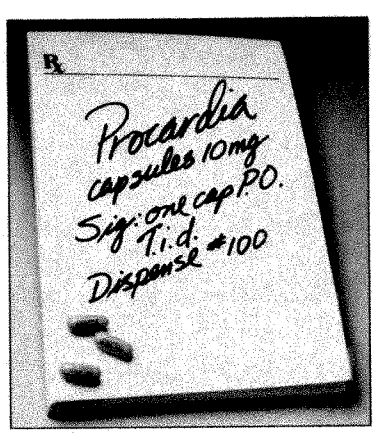
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Proven effective when used alone.

Enhanced effectiveness when combined with beta blockers.

Convenient dosing

Start with:	1	10-mg capsule *t.i.d.*
Titrate to:	2	10-mg capsules *t.i.d.*
Titrate to:	3	10-mg capsules *t.i.d.*



For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely. Maximum dose: 180 mg/day.

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PROCARDIA® CAPSULES
(nifedipine)

For Oral Use

BRIEF SUMMARY

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Increased Angina/Beta Blocker Withdrawal: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Pregnancy: Category C.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA Capsule contains 10 mg of nifedipine. PROCARDIA Capsules are supplied in amber glass bottles of 100 capsules (NDC 0069-2600-66).

The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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A Simple Teaching Device for Examination of the Arterial and Venous Pulse

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A simple teaching device is described for examination of the cervical arterial and venous pulses. It is a mechanical device that simultaneously generates a visible jugular venous pulsation and a palpable carotid arterial pulsation to train medical students, physicians, and paramedical personnel. Changing of cams allows the observer to appreciate these pulsations in the normal or in a variety of abnormal states. Graphic tracings of wave forms demonstrate the accuracy of reproduction of physiologic tracings. In a test of the device, cardiologists performed significantly better than medical students in the identification of unknown pulsations. The instrument is readily accepted, simple to operate, and fully portable.

As part of the physical examination, study of the vessels of the neck may yield a great deal of information. The pulsations of these vessels are the most proximal superficial indicators of the state of the heart and vascular system.[1-6] Assessment of these pulsations is a usual part of a thorough cardiovascular physical examination. The importance and value of properly identifying and interpreting pulsations of the neck veins and arteries has been recognized since at least the year 200 AD.[3] In present-day intensive care units pressures and wave forms are often measured directly by insertion of catheters attached to the transducers. In these days of medical cost containment, it is increasingly important that the physician be able to assess, screen, and diagnose as accurately as possible the condition of the heart at the bedside using only his or her own eyes, ears, and hands.

The variations of normal and the spectrum of abnormal pulsations are subtle and best perceived only by the experienced clinician. Traditionally, this experience has been derived exclusively from patient contact and examination requiring many years of training. The device is intended as an adjunct to this training. The device described herein is designed to mimic the visual pulsations of the internal jugular vein and the palpable pulsations of the carotid artery in both health and disease.

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The Instrument

Description: The device (Fig. 1) consists of 3 systems driven simultaneously by a single-gear motor. The mechanism mimicking the jugular venous pulse is on the right and the carotid pulse simulator is on the left. Small lights are used to mark the occurrence of the first and second heart sounds as well as any murmurs associated with pathologic conditions. The device does not reproduce these sounds audibly.

The position of the examiner is similar to that for an actual physical examination. Situated on the right side of the device, as in the bedside examination, the examiner places a finger over the anatomic position of the carotid artery. Visual attention is directed at the tubing representing the internal jugular vein. As in the live patient these pulsations should be viewed tangentially. The small lights are observed to mark the occurrence of heart sounds or any murmurs. Tactile stimuli from the arterial pulse as well as the heart sounds are used for proper identification and interpretation of venous pulsations.

The cams (Fig. 2) are carefully designed and shaped to reproduce accurately and reliably the various normal and abnormal pulsations. The accuracy of reproduction is demonstrated by graphic tracings (Fig. 3) obtained from the device with an external pulse recorder and comparison with knowledge of physiologic recordings from patients.[1-6]

The pulsations currently available are listed in Table I. Cams are easily changed within seconds to reproduce the desired abnormality.

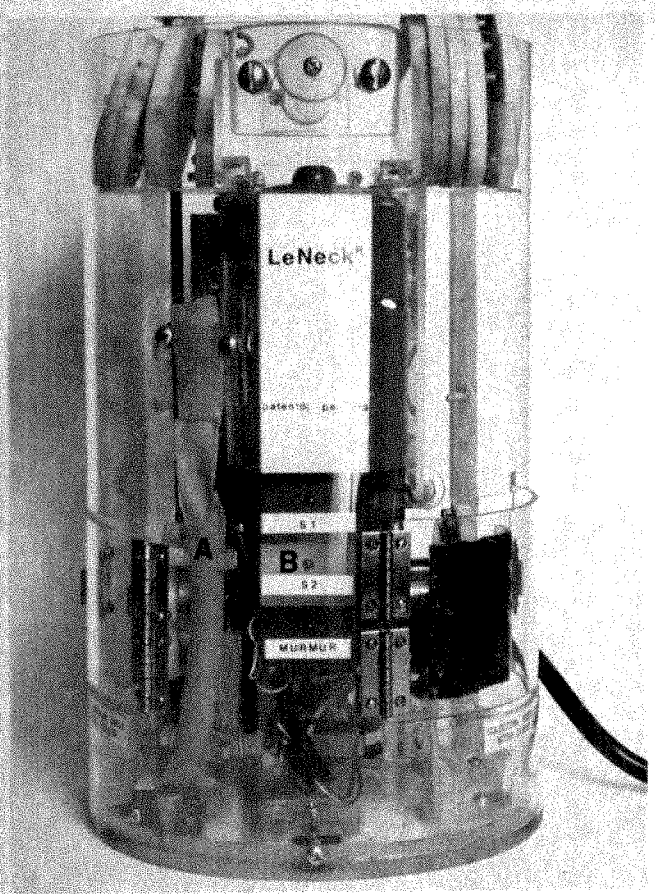

FIGURE 1. The instrument is the approximate size and shape of a human neck. **A**, visible venous pulsations. **B**, lights marking the occurrence of heart sounds. **C**, palpable arterial pulsations.

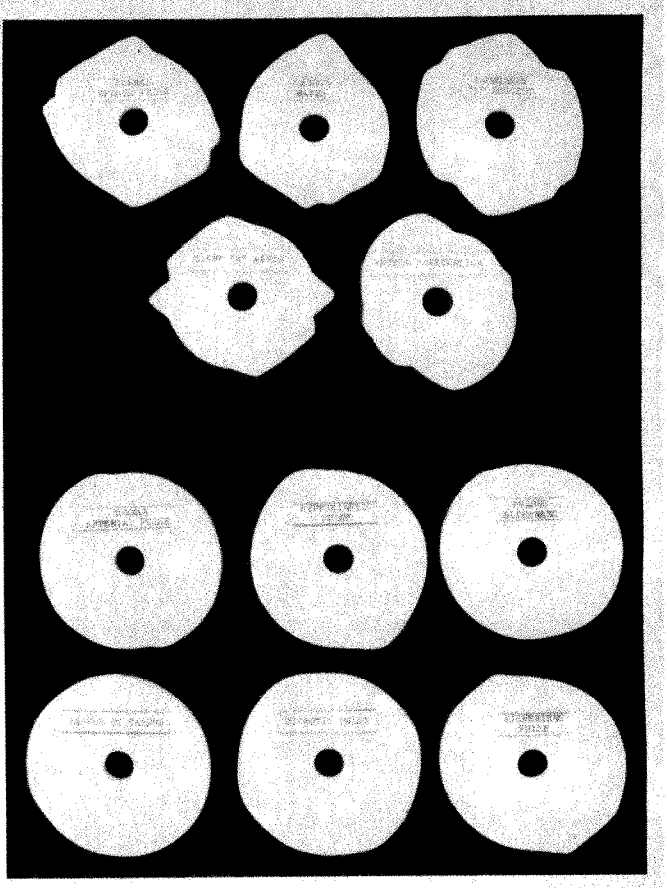

FIGURE 2. The cams are carefully shaped to reproduce the appropriate wave forms.

The device is designed to be portable and needs only a standard electrical outlet. Experience with medical students shows that the device is readily accepted and simple to operate.

Assessment: A study was performed to objectively assess this new teaching tool. Because it is logistically difficult to assess the learning of a physical examination skill, we elected to determine whether the device indicates a person's present level of that skill. We therefore compared the performances of a group of cardiologists with a group of third and fourth year medical students. Both groups have a knowledge and understanding of the pulsations. However, the cardiologists were certified by the Internal Medicine Board and had specialty training in cardiology and clinical experience.

TABLE I Number Correct for Each Pulse

	Cardiologists Correct (n = 11)	Medical Students Correct (n = 14)
Venous		
Cannon waves	11	7
Normal venous	4	5
Bogus	2	0
Giant *a* waves	5	9
Prominent *y* descent	7	5
Ventricularization	9	7
Arterial		
Dicrotic	8	10
Pulsus alternans	11	13
Normal arterial	10	12
Hyperkinetic pulse	11	13
Bisferiens pulse	9	7
Parvus et tardus	10	12

TABLE II Distribution of Scores (Number Correct Out of 12)

Score	Cardiologists (n)	Medical Students (n)
12	1	0
11	2	0
10	4	1
9	2	1
8	1	6
7	1	2
6	0	1
5	0	2
4	0	0
3	0	0
2	0	1
1	0	0
0	0	0
Total	11	14
Mean	9.73	7.07
SD	1.42	2.02
Var	1.84	3.78

F test of 3.18 ($p < 0.01$) and *t* test of 3.54 ($p < 0.01$) between mean scores of the 2 groups. SD = standard deviation; VAR = variance.

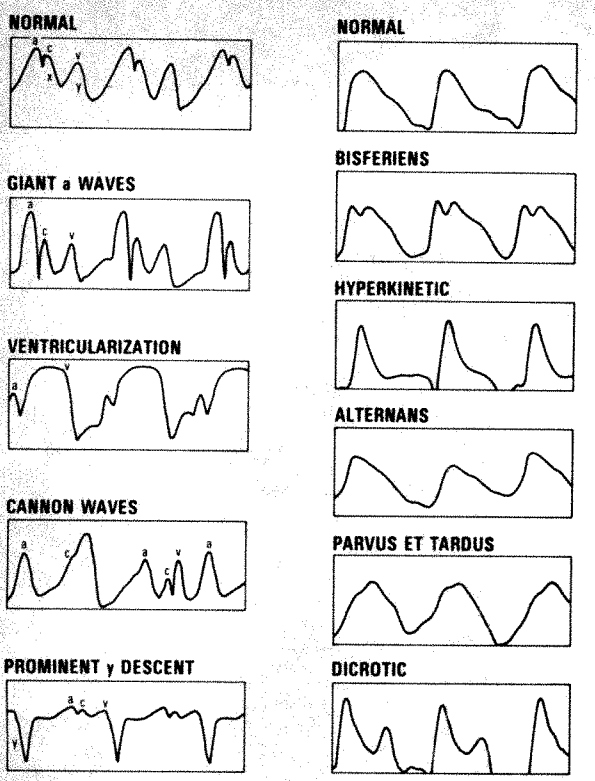

FIGURE 3. Neck venous (**left**) and arterial (**right**) pulses: graphic tracings of waves generated by the device, recorded with a clinical external pulse recorder.

Name labels on the cams were removed. Venous cams were labeled 1 through 6 and arterial cams were labeled 7 through 12. One cam (venous) was bogus. The examiner attempted to identify each arterial and venous pulse on a test sheet (Table I). All testing was supervised by the same person (AK). Each subject was given the following set of rules: (1) There is at least 1 (of the 12) bogus pulse; (2) no choice is used more than once; (3) you may return to any cam to recheck your answer; and (4) the variable speed control may be used. The device was initially set at a rate of 70 beats/min. Arterial pulsations were tested first. Then, the normal arterial cam was disclosed and used in the identification of the venous pulsations.

Results

Table II shows the distribution of scores (number correct out of 12) for each group. The cardiologists performed better than the medical students. The difference between the 2 groups is significant at the $p = 0.01$ level.

Table I displays the same data by pulse for each group. Analysis of these data shows several interesting points. There was a significant difference in the 2 groups interpreting venous pulsations but no significant difference in interpreting arterial pulsations. The largest differences between the groups occurred when the following pulses were tested: cannon waves, prominent y descents, ventricularization, and bisferiens pulse. The pulses most often correctly identified were the pulsus alternans and the hyperkinetic pulse. The pulses least often correctly identified were the bogus and the normal venous pulses; these were correctly identified by less than half in each group.

Analysis of individual test sheets showed that the most commonly confused pair were the double-peaked arterial pulses, bisferiens and dicrotic. This error was made by 2 cardiologists and 3 medical students.

Discussion

The results of the assessment demonstrate that trained cardiologists can effectively recognize most of the pulses mimicked by the device, and that training enhanced the identification of venous pulses mimicked by the device. The fact that a greater difference was seen when testing the venous than when testing the arterial pulsations may be attributed to a number of factors. Among these are greater ease in learning the arterial rather than the venous examination and technical factors involving the device or study.

A subjective conclusion that may be drawn from the present study is the acceptance of the device by the subjects. It was viewed as fun, worthwhile, and valuable. The device has shown itself to be practical and easily operated.

Conclusions: The device has been named "LeNeck" (patent pending). The design is original and unique. LeNeck is likely to be a useful teaching aid. Direct visualization of venous pulses and palpation of arterial pulses of rare prevalence will be especially useful to students with limited contact with uncommon abnormalities. The device is intended to be an adjunct to proper and thorough training of physicians and other health care professionals.

Acknowledgment: This device was developed as an independent medical student study project by Arthur Kreitenberg with support from the University of California, San Diego, School of Medicine, Office of Learning Resources.

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Evaluation of Pulmonary and Systemic Blood Flow by 2-Dimensional Doppler Echocardiography Using Fast Fourier Transform Spectral Analysis

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This study was designed to assess the accuracy and problems of noninvasively measuring right and left cardiac output by range-gated pulsed Doppler echocardiography. Sixteen children with cardiac disease, aged 3 months to 17 years, served as the subjects; 2-dimensional range-gated pulsed Doppler echocardiographic data were unobtainable in 2 children, leaving 14 for study. Diagnoses included shunt lesions, valvular abnormalities, coarctation, repaired defects, and Kawasaki's disease. The equipment for this study included a 2-dimensional echocardiographic Doppler sample volume locator. The Doppler frequency shift was analyzed by fast Fourier transform. Twenty 2-dimensional range-gated pulsed Doppler echocardiographic measurements (10 pulmonary and 10 aortic) were made simultaneously with indicator dilution outputs or angiographic outputs. In 4 subjects, 2-dimensional range-gated pulsed Doppler echocardiographic aortic outputs were not possible. For this study, vessel diameter was determined by both echocardiography and angiography, Doppler intercept angle by 2-dimensional echocardiography, and velocity by 2-dimensional range-gated pulsed Doppler echocardiography. Comparison of cardiac output measurements obtained by invasive methods and by 2-dimensional range-gated pulsed Doppler echocardiography (angiographic vessel measurement) showed a correlation of +0.94 (standard error of the estimate [SEE] = 0.53) with a slope of y = 0.83 × +0.61, indicating that the slope and line of identity were almost equal and the offset from 0 was small. For 2-dimensional range-gated pulsed Doppler echocardiography (echocardiographic vessel measurement), the correlation was +0.94 for aortic flow but only +0.72 for pulmonary flow. Problems encountered in some patients included turbulence, which made velocity measurements unreliable, difficulty in obtaining aortic flow by Doppler echocardiography due to transducer configuration, and measurement of pulmonary diameter by echocardiography. The results indicate that 2-dimensional range-gated pulsed Doppler echocardiographic outputs are accurate under conditions of nonturbulent or minimally turbulent flow and adequate imaging, but only when vessel diameter can be accurately measured.

Major interest in cardiac output measurement by Doppler echocardiography began 2 decades ago with the demonstration that circumferential Doppler flow probes could measure blood velocity. During the past decade, advances in echocardiographic technology provided the stimulus to adapt Doppler flow measurements to insonation of the aorta from the body surface. Four measurements necessary to compute blood flow by Doppler include (1) blood velocity; (2) vessel area; (3) intercept angle between the Doppler beam and flow; and (4) heart rate. Initial attempts to measure blood flow with Doppler concentrated on continuous wave devices. Although results obtained with these devices were remarkably encouraging, several problems were identified: (1) Continuous wave Dopper measurement provides velocity information from all along the Doppler beam. This nonselectivity permits simultaneous collection of velocity information from desired and undesired locations. (2) The angle of intercept between the Doppler beam and the direction of flow was uncertain. Beam

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TABLE I A Nonexhaustive Summary of Investigations Using Aortic or Pulmonary Flow Measurements or Approximations, or Both

Author	Population	Doppler Type	Frequency Analysis	Placement Doppler SV	Flow Comparison	Doppler Output	Measurement Site
Darsee et al[1]	20 dogs	CW	ZCD	Max signal	EM catheter	Volume flow	AO
Colocousis et al[2]	6 dogs	CW	Not stated	Max signal SSN or by direct placement on aorta	Thermal	Systolic velocity integral	AO
Sequeira et al[3]	20 human subjects	CW	Not stated	Max signal	ID, EM catheter	Volume flow	AO
Huntsman et al[4]	7 human subjects	CW	Kay sonograph envelope detector	Max signal	Not studied	Velocity	AO
Darsee et al[5]	29 patients	CW	ZCD	Max signal	Fick and thermal	Volume flow	AO
Griffith and Henry[6]	20 human subjects	Pulsed	True spectral	2D echo	None	Velocity	AO
Magnin et al[7]	11 human subjects	Pulsed	ZCD	2D echo	Fick, but at another time	Volume flow	AO
Steingart et al[8]	6 dogs	Pulsed	ZCD	Direct placement on aortic arch	EM	Systolic frequency shift integral	AO
Angelsen and Brubakk[9]	18 human subjects	Pulsed	Frequency estimation	Max signal	None	Velocity	AO
Goldberg et al	16 human subjects	Pulsed	FFT	2D Echo	ID	Volume flow	AO + PA

AO = aorta; CW = continuous wave Doppler; EM = electromagnetic; FFT = fast Fourier transform; ID = indicator dilution; max signal = maximal signal; PA = pulmonary artery; pulsed = range-gated pulsed Doppler; SSN = suprasternal notch; SV = sample volume; 2D echo = 2-dimensional echocardiography; ZCD = zero crossing detector.

direction was adjusted to record the maximal available signal and an angle of 180° was assumed. (3) Linear frequency analysis of the Doppler shift was technically difficult to measure, so a zero crossing detector was employed to plot a time interval histogram of the average flow at each point in time. Zero crossing detectors are nonlinear devices because they cannot provide frequency analysis of a spectrum, although they work acceptably well for analysis of a single frequency, particularly if the signal is strong and the noise level is low. Despite these problems, systolic velocity and frequency intergrals, true systolic velocity, and cardiac output were shown to be measurable by the Doppler method.[1–5] A nonexhaustive list of previous work is contained in Table I.

Recent advances in technology have allowed a new generation of equipment to become available, some of which promise to solve certain of these problems. Pulsing of the transmitted signal allows range-gating so that Doppler information can be obtained from an isolated area selected by M-mode or 2-dimensional echocardiography. Early work with range-gated cardiac output measurement[6–9] is also summarized in Table I. Unfortunately, this advance causes the loss of detection of very high velocities which were possible with continuous wave Doppler but not with pulsed Doppler echocardiography. If the Doppler sample is located with 2-dimensional echocardiography, the angle between flow and the Doppler beam can be determined in 2 planes. Additionally, 2-dimensional echocardiography allows estimation of great vessel diameters. Finally, Doppler frequency shift can now be analyzed by fast Fourier transform, a technique that provides linear analysis at a present repetition rate of 200 samples/s. However, to date, we are unaware of published data that compare aortic or pulmonary blood flow, or both, as measured with this new generation of Doppler instrumentation, with blood flow measured with standard techniques.

The purpose of our study was to simultaneously measure right or left heart output in patients with (1) a range-gated pulsed Doppler device capable of frequency analysis by linear fast Fourier transform analysis, the sample volume of which was located with 2-dimensional echocardiography, and (2) an invasive technique for cardiac output determination, principally indicator dilution, for the purpose of comparing results of the 2 methods. A secondary purpose was to detail the problems encountered during Doppler cardiac output measurement.

Methods

The population consisted of 16 children who were undergoing clinically indicated cardiac catheterization. Diagnoses of individual patients is shown in Table II. Children with complex anomalies were excluded. This group of children was selected to allow accurate invasive determination of cardiac output by indicator dilution. A prototype range-gated pulsed Doppler unit (Electronics for Medicine, Honeywell) was used. This instrument provided a 2.5 MHz real-time 2-dimensional image achieved by sweeping a conventional single element transducer through a 60° arc. The equipment also provided an electrocardiographic trace, and a frequency analysis of the Doppler signal by fast Fourier transform.

The sample volume is the area within which the velocity of blood flow is sampled by the Doppler. In the prototype instrument, an adjustable position Doppler sample volume of operator-selectable length could be positioned along any information line of the 2-dimensional image. The width of the sample was determined by beam width at any sampling depth and was not under operator control. The location on the 2-dimensional image at which Doppler would be sampled was

TABLE II Individual Patient Data

Case	Diagnosis	Cardiac Output Doppler (Angio)	Doppler (Echo)	Invasive	Pulmonary Output Doppler (Angio)	Doppler (Echo)	Invasive CO
1	ASD primum	1.05	1.05	0.89	3.04	3.20	3.56
2	TOF (PO)	3.42	2.80	2.94	...	...	...
3	Kawasaki's	2.45	1.45	2.39	3.23	2.68	2.39
4	TI, trivial	2.52	2.88	3.78	4.10	3.63	3.78
5	Coarct	3.58	2.68	3.02	...	...	...
6	VSD	1.23	1.87	1.30	1.64	2.31	1.50
7	TOF (PO)	6.70	6.70	6.25	...	...	...
8	VSD	4.29	3.69	3.76	3.77	4.43	4.40
9	TOF (PO)	4.09	5.68	4.00	...	...	...
10	Coarct	4.02	3.84	3.62	4.09	5.68	3.84
11	AS, AI	...	...	...	8.59	4.89	7.67
12	AS	...	...	...	2.41	3.11	3.35
13	AS	...	...	...	6.07	4.75	5.50
14	VSD (PO)	...	...	...	2.79	3.16	3.58

Note that each patient did not necessarily have an aortic and pulmonary flow measurement. AI = aortic insufficiency; angio = diameter measured by angiography; AS = aortic stenosis; ASD = atrial septal defect; CO = cardiac output; coarct = coarctation of the aorta; echo = diameter measured by echocardiography; PO = postoperative; TI = tricuspid insufficiency; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

determined by automatically highlighting an information line within the 2-dimensional image along which the transducer would stop when the operational mode was switched from 2-dimensional echocardiography to range-gated pulsed Doppler. The depth and length of the sample volume were also superimposed on the image and on the Doppler outputs (Fig. 1). The Doppler sampling rate was 19,500 samples/s (maximal velocity ± 331 cm/s) at 0 to 4 cm and 9,750 samples/s at 4 to 8 cm (maximal velocity ± 161 cm/s). Once in the Doppler mode, 2 simultaneous outputs were available. The first was an audio signal, and the second was a fast Fourier transform spectral analysis of the Doppler signal which was sampled 200 times/s. Dopper output and an electrocardiographic tracing were recorded on a strip chart. The output of the fast Fourier transform was calibrated in Doppler shift frequency (Hertz) and directly converted by the instrument to velocity of flow calibrated in cm/s according to the following formula: Velocity = frequency shift × velocity of sound in the medium/2 × transmitted frequency × cos θ, where θ = the angle of incidence between the Doppler beam and flow direction.

Ultrasonic studies performed in the catheterization laboratory during the invasive procedure began with 2-dimensional imaging of the pulmonary artery from a precordial short axis transducer position. Images in this plane consist of the ascending aorta in cross-section and a long axis of the right ventricular outflow tract, main pulmonary artery, and its bifurcation. Once the appropriate image was found, the highlighted Doppler interrogation line was placed distal to the pulmonary valve and as parallel as possible to the center of the main pulmonary artery, and the Doppler sample volume was adjusted to 5 to 10 mm in length (Fig. 1). Care was taken to maintain the transducer in a steady position and the output of the fast Fourier transform was examined visually. Frequently, some transducer adjustment was necessary to optimize the recorded Doppler output within the main pulmonary artery. After an optimal Doppler signal was found and the Doppler interrogation line was confirmed to be within the main pulmonary artery, a 2-dimensional frame, gated in early systole, was photographed to verify the Doppler position and to allow later determination of the Doppler-flow intercept angle. The diameter of the pulmonary was measured, when possible, on this image with leading edge methodology at a portion of its sweep around the aorta near the insertion of the pulmonary valve where the vessel would be measured axially. However, in many patients axial measurement was impossible and an image similar to the one in Figure 1 was recorded. In these instances, gain was reduced until the walls of the pulmonary artery were as thin as possible and the measurement was made from inner to inner wall (no leading edges exist in this instance).

Next, the transducer was placed in the suprasternal notch, the ascending aorta was imaged, and the Doppler interrogation line was directed into the ascending aorta. The aortic diameter used for calculating aortic area by echocardiography was measured from M-mode traces of the aortic root derived from the short-axis 2-dimensional image. Sample volume length, beam positioning, and recording procedures were essentially similar to those already described for the main pulmonary artery.

Analysis of records: Cardiac output was computed according to the formula: Cardiac output = (mean velocity/beat × heart rate × vessel area)/cos θ. Mean velocity was measured by tracing the middle of the densest portion of the gray scale display output of the spectral analyzer along the systolic phasic velocity curve with an Apple computer (Cupertino, California) and a commercially available program (Biodata, Davis, California). For ≥5 beats, the velocity area was computed and this integral was divided by the average beat duration to provide the mean velocity. Mean heart rate for these beats was measured from the R-R interval. Great vessel diameter in each patient was measured from 2-dimensional echocardiographic images or the derived M-modes as just described and also from calibrated angiographic contrast studies of the great arteries obtained during the same catheterization procedure. Flow was assumed to be directed along the axis of the great vessel. The intercept angle between the Doppler beam and blood flow in the vessel was measured. Because 2-dimensional echocardiography was used to determine this angle within the plane, the angle between flow and Doppler interrogation in the third nonvisualized (elevational or azimuthal) plane was not taken into account.

Cardiac output by Doppler measurement was compared with simultaneous measurements by indicator dilution (thermal, 2 patients; Fox green dye, 17 patients) or in 1 instance by an angiographic technique as an average of the first 3 beats.

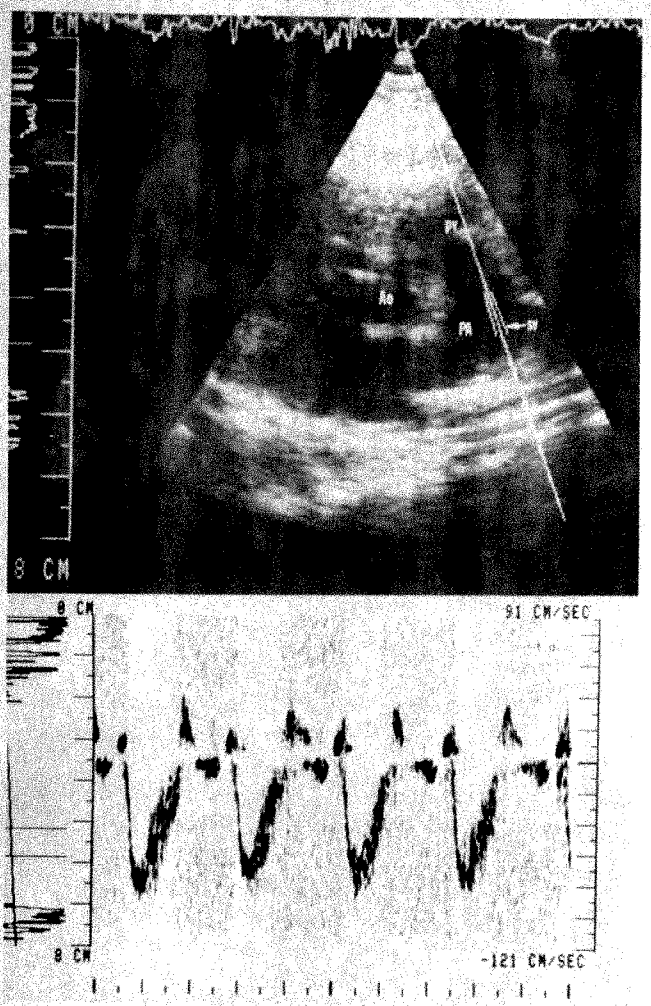

FIGURE 1. Top, a 2-dimensional echogram showing a small area of right ventricular outflow, pulmonary valve (PV), and main pulmonary artery (PA) and its branches. The sample volume (SV), shown by **parallel bars** flanking the Doppler indicator line, is in the main pulmonary artery. In this instance, we could not measure the pulmonary artery by axial resolution and the arterial borders are present but indistinct. This example demonstrates the problem with echocardiographic measurement of the pulmonary artery diameter. The **bottom panel** shows calibrated velocity within the pulmonary artery. Tracing of velocity for integration is obvious on the downslope; however, the precise area for tracing on the upslope is less obvious. We traced the center of the dense area on the upslope. The electrocardiogram is not shown on this velocity tracing. Ao = aorta.

Right or left ventricular outputs by indicator dilution were determined by the logarithmic extrapolation technique. Right heart output was measured by injecting into the pulmonary artery and sampling in the left atrium, left ventricle, or aorta, but always proximal to a shunt. Left cardiac output was measured by injecting into the pulmonary artery, left atrium, or left ventricle, and sampling in the aorta. Thermal cardiac outputs were measured in 2 patients without shunts by injecting cold saline solution into the right atrium and sensing the temperature change in the pulmonary artery. One patient had an angiographic cardiac output determined by modified Simpson's rule.[10] The angiographic and thermal techniques used in our laboratory show a variance of ±7% when compared with the green dye technique.

Results

Adequate imaging and Doppler data were obtained in 16 patients aged 3 months to 17 years. No patient had a velocity that exceeded the maximal velocity limits. Results of 2 patients were excluded because cardiac output measurement by indicator dilution was impossible because of blood withdrawal pump failure, leaving 14 patients in whom simultaneous Doppler and conventional cardiac output measurements could be made. In 4 instances, aortic flow measurement could not be made because of inability to image the ascending aorta adequately from the suprasternal notch. Doppler measurement of pulmonary flow was not attempted in 3 patients who had pulmonary valvular insufficiency. Pulmonary flow was not measured in another patient because of equipment failure after the aortic flow measurement. Data for each patient are shown in Table II.

Doppler measurement technique: The Doppler intercept angle with the great vessel, as imaged in 2 planes, proved easy to measure. Tracing the center of the densest portion of the velocity curve also proved to be easy and highly reproducible from person to person unless turbulence caused marked spectral dispersion. In that event, tracing was impossible. Aortic diameters were highly reproducible, but pulmonary artery diameters were difficult to measure. Figure 1 illustrates this problem. This image is representative of most of the patients. The anterior left border was frequently ill-defined, and the wall next to the aorta was only slightly more distinct. Variation in pulmonary artery size between frames of this patient measured 3.8 mm, a number representative of the entire group.

Flow measurements by Doppler using angiographically determined vessel diameter (Fig. 2): Flow, measured by Doppler in the pulmonary artery and aorta using angiographically determined vessel area and invasively measured flow, was statistically similar by Student's t test. The correlation between the 2 output measurement techniques was r = +0.94, SEE = 0.53 liters/min (Table III) for combined pulmonary and aortic measurements. Combination was appropriate because the individual correlation coefficients for the comparison of Doppler and invasive cardiac outputs were equal for pulmonary (r = +0.94) and aortic (r = +0.94) flow and because the respective slopes and intercepts were quite similar (0.86 and 0.31 [cardiac output] and 0.79 and 0.80 [pulmonary output]).

Doppler cardiac output measured with echocardiographically determined vessel diameter (Fig. 2): The correlation coefficient (r = +0.86) for invasively measured output and combined pulmonary and aortic Doppler determined output, using ultrasonically determined vessel size, was lower than that for Doppler flow obtained from angiographically determined diameters. Furthermore, the standard error of the estimate for the relation with vessel diameters measured by echocardiography was 830 ml, which was about 50% greater than the standard error of the estimate for vessel

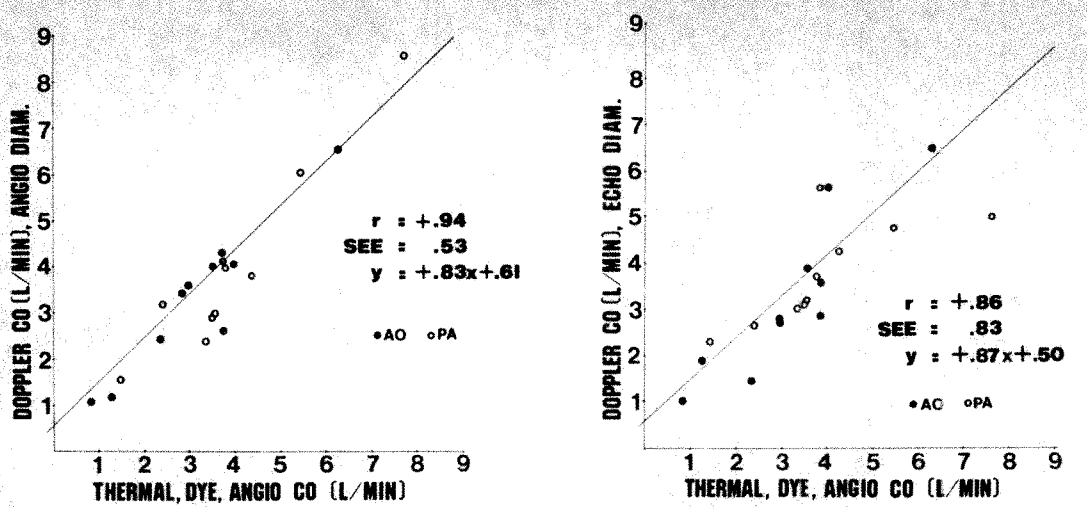

FIGURE 2. Left, results of Doppler cardiac output (CO) determined by angiographically determined vessel diameter (ANGIO DIAM) are compared with cardiac output determined by invasive measurements. **Right,** this illustration is essentially similar except that Doppler cardiac output was computed with vessel diameters measured from echocardiograms. SEE = standard error of the estimate (in liters/min); y = 0.83x +0.61, y = 0.87x +0.5 are slope formulas; other abbreviations as in Figure 1.

size determined by angiography. The correlation between cardiac output determined invasively and Doppler output determined with echocardiographically measured vessel diameter was poorer for the pulmonary artery (r = +0.72) than for the aorta (r = +0.91). This lower correlation for pulmonary flow resulted from the difficulty in measuring the pulmonary artery diameter by either 2-dimensional or M-mode echocardiograms derived from the 2-dimensional image, whereas the aortic diameter was relatively easy to measure.

Discussion

The unique feature of this investigation was that simultaneously measured range-gated pulsed Doppler pulmonary or systemic flows were compared with flows measured by accepted invasive techniques, principally the indicator dilution technique. Furthermore, in this study, spectral analysis of range-gated pulsed Doppler flow was accomplished by fast Fourier transform, which provided an accurate and linear frequency analysis of the Doppler signal. Our results indicate that the combination of 2-dimensional echocardiographic location of the Doppler sample volume, use of fast Fourier transform analysis, and accurate measurement of the vessel diameter provides right or left heart outputs that were comparable to values determined by commonly used invasive techniques.

Problem of pulmonary artery flow measurement: The major problem encountered during this investigation was the measurement of pulmonary artery diameter by echocardiography. Although the pulmonary artery could be imaged in several patients so that axial measurement of diameter was possible, in the remainder we obtained images similar to that shown in Figure 1. In this instance, the pulmonary artery is imaged mainly by lateral resolution and the borders are unclear.

TABLE III Correlation of Different Techniques for Measuring Cardiac Output*

Technique		Compared With	r	SEE	Slope	Intercept
Doppler CO	(Angio diameter)	CO invasive technique	0.94	0.46	0.86	0.31
Doppler CO	(Echo diameter)	CO Invasive technique	0.91	0.60	0.76	0.70
Doppler CO	(Angio diameter)	Doppler CO (echo diameter)	0.90	0.75	0.98	0.00
Doppler PO	(Angio diameter)	PO invasive	0.94	0.51	0.79	0.80
Doppler PO	(Echo diameter)	PO invasive	0.72	1.11	1.11	−0.23
Doppler PO	(Angio diameter)	Doppler PO (echo diameter)	0.70	0.75	0.378	2.28
Doppler P + S output	(Angio diameter)	P + S invasive	0.94	0.51	0.83	0.61
Doppler P + S output	(Echo diameter)	P + S invasive	0.79	0.95	0.87	0.50
Doppler P + S CO	(Echo diameter)	Doppler P + S CO (angio diameter)	0.75	0.94	0.62	1.21

* All correlation coefficients are positive and significant at $p < 0.001$. The correlation (r), standard error of the estimate (SEE), slope, and intercept for each relation are listed. For example, the first data is a comparison of (1) cardiac output by Doppler with vessel measurement by angiography, and (2) cardiac output measured invasively.

Note: These data show that echocardiographically measured pulmonary diameters produce lower correlation of Doppler and invasive cardiac outputs than do echocardiographically measured aortic diameters. angio = angiographic; echo = echocardiographic; CO = cardiac output; PO = pulmonary output; P + S = pulmonary plus systemic.

Measurements of the diameter on different frames of the same person varied by 3.8 mm. Such imprecision is a major problem, for the diameter divided by 2 must be raised to the second power to compute vessel area. This error in vessel size on echocardiography caused the low correlation (+0.72) of measured flow and Doppler flow. Furthermore, we studied the pulmonary size in children in whom better images are usually recorded than those in adults. A more accurate estimate of pulmonary artery size, obtained by angiography, improved the correlation to +0.94. Improved echocardiographic resolution may reduce this problem but will never solve it. Currently, an angiographic vessel measurement is necessary for very high correlation of pulmonary flow measured by pulsed Doppler and by invasive techniques. Obtaining pulmonary flow velocity was never a problem.

Problem of aortic flow velocity measurement: Aortic flow velocity measurement was not possible in 4 patients because the transducer was physically too large to place in the suprasternal notch. In several other patients, appropriate imaging was achieved only with hyperextension of the neck and considerable effort. Echocardiographic measurement of the diameter of the ascending aorta was not a problem, as borne out by the similarity of correlation for flow with an aniographic aortic measurement (+0.94) and an echocardiographic aortic measurement (+0.91).

All correlations were obtained over a large span of cardiac outputs in children ranging in age from 3 months to 17 years. The correlation might not be as good in a group of adults of uniform size.

Angular measurements: On the assumption that flow generally paralleled the ascending aortic walls, we determined the angle between the walls and the Doppler beam. This measurement proved to be easy and repeatable. Furthermore, if the intercept angle was within 20° of the flow axis, the error introduced by imprecise measurement would be small. Angular measurement could prove to be a significant problem if other echocardiographic planes, such as the subcostal, were used because the angle of the third, but unobserved, plane could be large.

Experience with fast Fourier transform: Spectral analysis by fast Fourier transform introduces a problem not encountered with time interval histography. With time interval histography, only the average frequency for a given time period is recorded. This characteristic makes time interval histography highly vulnerable to disturbed flow; consequently, the results of disturbed flow measurement will be very alinear.[11] Furthermore, with time interval histography, for any discrete time interval, frequency does not appear to have width. Fast Fourier analysis, however, allows display of all contained frequencies at each time interval. The analyzer used in this study depicted, for each time interval, the amplitude of the energy at each frequency as a shade of the gray scale, so that the highest recorded energies were more toward the black end of the scale and the lowest energies more toward the white. We elected to integrate the velocity curve by tracing the center of the darkest portion of the curve containing the most common frequency shift. This is a compromise. Merely averaging the spectrum for Doppler analysis would allow random turbulent velocities to be overemphasized. Tracing the center of the darkest part of the spectrum allows slight subjectivity, but interobserver variability on the same tracing was insignificant. The reasons that interobserver differences are so slight are (1) the technique is easy to apply, and (2) the mean integral is used in the computation. Use of the mean integral reduces minor interobserver tracing differences.

Comparison of results with those of other investigations: In this investigation, cardiac output determined by Doppler echocardiography and by invasive techniques demonstrated a better correlation than that reported by Magnin et al,[7] who also used a 2-dimensional sample volume locator. In their investigation, spectral analysis was performed by time interval histography. Their results showed a useful correlation ($r = +0.83$), but the slope of the regression line was 0.6x with a major offset (about 3.3 liters/min). By comparison, the fast Fourier transform used in this study to determine frequency shifts is essentially a linear system,[11] and this linearity probably permitted the better results presented in this study. Our results with visually directed placement of the Doppler sample volume approximate those of aortic outputs obtained with continuous wave Doppler,[1–3,5] but we regard as highly preferable the placement of a range-gated pulsed Doppler sample volume into a known vessel location defined by 2-dimensional echocardiography, because great vessels, particularly in patients with congenital cardiac disease, may occur in unexpected locations and have unusual courses. Furthermore, with continuous wave Doppler, the Doppler shift throughout the entire ultrasound beam is sampled and the result is a summation of all received Doppler signals. Accordingly, the sample may include additional and undesired atrial or ventricular velocities. With range-gated pulsed Doppler, velocity is sampled exclusively in the area of interest.

Flow profiles: In this investigation we assumed that the flow profile in or near the center of a large vessel was approximately flat, that is, that flow velocity was uniform across most of the vessel diameter. This was an important consideration, for if the flow profile had any other shape, positioning of the area sample volume would be critical, and unless the exact profile were known, the output could not be determined reliably from a single sample. A flat flow profile in large vessels is consistent with theory and results obtained by others.[12] In some patients mild to moderate flow disturbances were detected as a broadening of the spectral pattern. Under conditions of flow disturbance, the broadening of the curve observed with fast Fourier transform is markedly less than that observed with time interval histography.[13] In this study a recognizable and traceable forward flow velocity curve was still obtainable despite some flow disturbance in all but 1 instance. If frequency broadening obscured the forward flow

curve, no flow was computed. Results in those patients with mild flow disturbances, when compared with those of the invasive measures, were not different from results for the group as a whole.

Maximal velocities: The maximal velocity recorded in our patients did not exceed the maximal velocity for the given depth of interrogation; however, velocities exceeding the maximal detectable velocity do occur, particularly in patients with high flow or jets. The reason we did not encounter this problem is that we worked within 0 to 8 cm of the transducer. These close ranges will not be possible in all patients. Maximal velocity is limited mainly by the transmitted frequency and the pulse repetition frequency, the latter of which, in turn, is determined by the depth of the sample. Maximal velocity is usually expressed as the velocity on either side of zero; for example, ±110 cm/s measures a velocity span of 220 cm/s. It is currently unclear whether the span from 220 cm/s to zero is equivalent to ±110 cm/s. We did not utilize the total span on 1 side of zero in this study.

In conclusion, on the basis of our results, range-gated pulsed Doppler flow analysis using 2-dimensional echocardiography for sample volume location and intercept angle measurement and Fourier transform spectral analysis appears to provide clinically useful measurements of cardiac output if vessel diameter can be determined. However, numerous problems were encountered. Continued technical research into smaller transducer configurations, which might be useful in the suprasternal notch, and into techniques for improving imaging of the pulmonary artery should allow reliable, accurate measurements of great vessel blood flows.

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The Isovolumic Index: A New Noninvasive Approach to the Assessment of Left Ventricular Function in Man

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Both a high ratio of preejection period (PEP) to left ventricular ejection time (LVET) and a prolonged isovolumic relaxation time are associated with left ventricular dysfunction. In pilot studies in instrumented dogs, we measured a combined isovolumic index, defined as (isovolumic contraction + isovolumic relaxation time)/LVET and found an inverse correlation with changes in fractional shortening. To test the utility of this index in human subjects, we used the electrocardiogram, mitral valve (MV) echogram, and indirect carotid arterial tracing to calculate isovolumic index as (time from R wave to MV opening − LVET)/LVET × 100%. Normal subjects had isovolumic index values that averaged 24 ± 7% (standard deviation), in contrast to patients with cardiomyopathy who averaged 65 ± 14% ($p < 0.001$ versus normal values) and patients with coronary artery disease who averaged 40 ± 15% ($p < 0.001$ versus normal values and patients with cardiomyopathy). All normal subjects had an isovolumic index of ≤32% and all patients with cardiomyopathy had values >32%. Of patients with coronary artery disease, 72% (21 of 29) had an isovolumic index >32%. An isovolumic index >32% identified 20 of 22 patients (91%) with a reduced ejection fraction and 12 of 14 (86%) with a segmental wall motion abnormality, and it was a more sensitive marker of these abnormalities than abnormal E point-septal separation. In 6 patients with coronary artery disease who had simultaneous echocardiograms and measurements of left ventricular pressure by micromanometer tip catheter, the time constants of isovolumic pressure decrease were uniformly increased in association with an isovolumic index >32%. In contrast, all had normal PEP/LVET ratios. The isovolumic index is thus a sensitive, potentially useful noninvasive marker of left ventricular dysfunction that is easily obtained from the routine echocardiogram.

It has long been appreciated that in patients with left ventricular myocardial disease the period of isovolumic contraction is often lengthened whereas the ejection time is diminished.[1-3] When the preejection period is used as an estimate of the isovolumic contraction time, the ratio of preejection period to left ventricular ejection time can provide a useful index of abnormal left ventricular performance which has been correlated inversely with cardiac output, stroke volume, and fractional shortening.[2,4] More recently a number of studies have demonstrated that indexes of myocardial relaxation are frequently abnormal in patients with left ventricular myocardial disease.[5-14] We therefore postulated that a ratio of the sum of isovolumic contraction and relaxation times to left ventricular ejection time might be a sensitive index for the identification of left ventricular dysfunction. In pilot studies in dogs, described subsequently, this ratio did show an inverse correlation with fractional shortening. Accordingly, we then used a simple echocardiographic technique to derive the ratio and tested whether it would detect differences among a population of normal subjects, patients with coronary artery disease, and patients with congestive cardiomyopathy. We also assessed the sensitivity, specificity, and predictive accuracy of this ratio in detecting familiar markers of left ventricular dysfunction (wall motion disorder, depression of the ejection fraction, and abnormalities of myocardial relaxation) and compared the ratio to 2 other noninvasive indexes of left ventricular

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dysfunction, echocardiographic E point-septal separation and the preejection period/left ventricular ejection time ratio (PEP/LVET).

Methods

Animal studies: Six adult mongrel dogs were anesthetized with intravenous morphine sulfate (3 mg/kg) and alpha chloralose (90 mg/kg). The dogs were intubated and respiration was maintained with a Harvard respirator. The heart was exposed through a median sternotomy and suspended in a pericardial cradle. Pacing electrodes were sutured to the left atrium, and propranolol (1 mg/kg) was administered intravenously. Fluid-filled catheters were placed in the left atrium through a pulmonary vein and in the left ventricle through a femoral artery. These catheters were connected to Statham P23Db transducers with zero reference at the level of the right atrium. A Konigsberg P20 micromanometer was then inserted through the left atrial appendage into the left ventricle. The pressure obtained from the micromanometer was matched to that from the fluid-filled catheter. The latter was then withdrawn to a position just above the aortic valve to provide a recording of central aortic pressure. The micromanometer was frequently checked for drift by comparing peak left ventricular systolic pressure to peak aortic pressure. An inflatable occlusion cuff was then placed about the inferior vena cava. Finally, a pair of 5 MHz piezoelectric crystals (1.5 mm in diameter) were inserted through stab wounds in the left ventricular myocardium to the mid-wall depth approximately 1 cm apart. The crystals were placed at the midpoint, perpendicular to the ventricular long axis, and connected to a sonomicrometer-amplifier system for measurement of the shortening of a segment of myocardium oriented with the hoop axis fibers. The sonomicrometer was calibrated with a signal of known delay after the completion of each study. Atrial pacing at rates of approximately 10 beats/min greater than the basal rate was then initiated to maintain heart rate constant during the rest of the experimental protocol. To vary left ventricular preload and fractional shortening, the caval occlusion cuff was first inflated until end-diastolic pressure was 5 mm Hg or less. The cuff was then deflated in small increments with a data point obtained after each deflation. Once the cuff was completely deflated, an intravenous infusion of dextran in saline solution was begun to increase end-diastolic pressure to the 15 to 20 mm Hg range. Data were obtained at 3 to 7 points as left ventricular end-diastolic pressure was increased to this level.

All data were recorded on a polygraph (Brush Clevite, model 2000) and analyzed at a paper speed of 200 mm/s with respiration suspended at end-expiration. Five cardiac cycles were averaged for each measurement.

Four discrete timing events were measured. Left ventricular end-diastole was defined as the nadir of the pressure tracing after the *a* wave of the high gain left ventricular pressure tracing. Aortic valve opening and closure were defined by the aortic pressure recordings from the upstroke and dicrotic notch and transposed to the micromanometer tracing. Mitral valve opening was determined by the pressure cross-over points of the left atrial and left ventricular pressures. Fractional segment shortening was calculated as the difference between segment length at aortic valve opening and closure divided by segment length at aortic valve opening.

The isovolumic index (IVI) in these animals was defined as the sum of the duration of isovolumic contraction (IVC, from end-diastole to aortic valve opening) and isovolumic relaxation (IVR, from aortic valve closure to mitral valve opening) divided by the left ventricular ejection time (LVET) and expressed as a percentage: IVI (%) = [(IVC + IVR)/LVET] × 100.

Clinical studies: *Patient population:* The normal group consisted of 14 subjects; 6 were volunteers, 7 had been referred for the evaluation of innocent murmurs, and 1 had an echocardiogram performed before cardiac catheterization for the evaluation of atypical chest pain. Catheterization subsequently revealed no hemodynamic, left ventricular, or coronary angiographic abnormalities. All subjects had normal results on physical examination. None was taking any medication at the time of study and all had normal M-mode and 2-dimensional echocardiographic examinations. The mean age of this group was 31 ± 13 (SD) years (range 17 to 61). Resting heart rates ranged between 51 and 90 beats/min (mean 66 ± 10) and the blood pressure was 120/77 ± 18/9 mm Hg.

The cardiomyopathy group included 12 patients ranging in age from 34 to 70 years (mean 54 ± 10). All had dilated forms of cardiomyopathy with chronic, stable symptoms of congestive heart failure. The cause was ischemic in 10 and idiopathic in 2. One patient was not receiving medication at the time of the study. All others were taking digoxin and diuretics. Six of the 12 were receiving prazosin, 3 were ingesting nitrates, and 1 was also taking hydralazine. Two patients were receiving concomitant oral amrinone therapy. All 12 patients were in sinus rhythm with rates ranging between 58 and 99 beats/min (mean 79 ± 14), while the blood pressure was 113/72 ± 14/13 mm Hg. No patient had clinical evidence of valvular disease. Resting equilibrium radionuclide angiography was performed in all of these patients for measurement of ejection fraction.

The group with coronary artery disease included 29 patients, of whom 8 had undergone diagnostic cardiac catheterization within 2 weeks of the echocardiographic study. Seven patients were studied within 48 hours of catheterization, and 6 patients underwent echocardiography at the time of cardiac catheterization. All 21 catheterized patients had evidence of significant coronary artery disease as defined by angiographic luminal narrowing of 70% or more in at least 1 major vessel. The other 8 patients with coronary artery disease had either a history of a myocardial infarction (as evidenced by a typical history, diagnostic changes in creatine kinase levels, and evolution of persistent electrocardiographic signs) or a history of chronic, stable angina with diagnostic electrocardiographic or reversible thallium-201 scintigraphic abnormalities, or both, during exercise. Six of these 8 patients also had resting gated radionuclide ejection fraction determinations. Echocardiographic and radionuclide examinations were carried out at least 6 months after acute infarction in this group, and in all cases ischemic symptoms were stable. One patient with coronary artery disease was receiving digoxin at the time of study and 18 were taking beta-blocking drugs. Ages ranged from 24 to 69 years (mean 53 ± 12). During echocardiographic study the blood pressure was 131/79 ± 27/16 mm Hg and the heart rate was 66 ± 13 beats/min (range 46 to 90). No patient had evidence of valvular disease.

The 3 groups were not different with respect to blood pressure, but both groups of patients had a higher mean age than that of normal subjects ($p < 0.001$) and the mean heart rate in the cardiomyopathy group was higher than that in the other two groups ($p < 0.025$).

Methods: All patients underwent M-mode echocardiography using a Toshiba SSH-10A sonolayergraph with a Toshiba strip chart recorder. Each normal patient and all patients with cardiomyopathy also had 2-dimensional echocardiographic

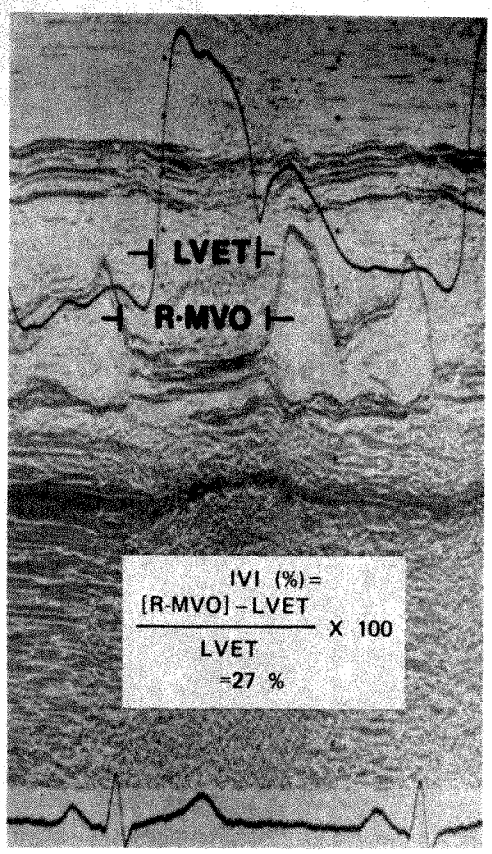

FIGURE 1. Calculation of the isovolumic index (IVI) from the simultaneous carotid arterial pulse tracing and mitral valve echocardiogram is demonstrated in a normal patient. LVET = left ventricular ejection time; R-MVO = the time from the peak of the R wave to mitral valve opening. **Dotted time markers** are at intervals of 500 ms.

examination using a 78° electronic phased array transducer to exclude unsuspected segmental wall motion abnormalities or valvular disease such as mitral valve prolapse. Simultaneous carotid arterial pulse tracings were recorded using a Fukuda model TY-303 transducer.

In the 6 patients with coronary artery disease who had echocardiographic examinations during cardiac catheterization, simultaneous left ventricular pressure was measured with a micromanometer tip high-fidelity catheter (Millar). Pressures were acquired on-line onto computer tape. Left ventricular pressure was also displayed on the echocardiographic strip chart paper and by using calibration signals, the specific high fidelity pressure tracing corresponding to simultaneous echocardiography events could be identified. This approach eliminated the need to hand-digitize the left ventricular pressure recording from high speed recordings so that the Toshiba strip chart recorder could be run at 50 mm/s. At this speed the mitral valve echocardiogram was not excessively expanded.

The mitral valve echocardiogram was obtained with the transducer in the second to fifth intercostal spaces and within 3 to 4 cm of the left sternal border such that maximal excursion of the mitral valve leaflets was recorded. The onset of mitral valve opening was taken from the onset of the most rapid anterior motion of the anterior mitral valve leaflet[15] (Fig. 1).

A suitable limb electrocardiographic lead was selected which showed a sharp R wave and this was recorded simultaneously on the strip chart. No patient had evidence of bundle branch block.

The isovolumic index was determined as follows. The left ventricular ejection time was taken from the onset of the most rapid upstroke of the catorid arterial pulse tracing to the dicrotic notch. The period from the peak of the R wave to the mitral valve opening (R-MVO) was then determined. We chose the peak of the R wave from which to measure the interval of total electromechanical systole and isovolumic relaxation (R-MVO) because in our experience it was more easily reproducible than the onset of the Q wave, particularly in tracings recorded from the echocardiographic strip chart, in which gain and lead selection are limited. Subtracting left ventricular ejection time from R-MVO gives an interval that includes isovolumic contraction, isovolumic relaxation, and a small interval of electromechanical delay. Therefore, this measure provides an estimation of the time during which the left ventricle is in an isovolumic state and is termed the *isovolumic time* (IVT). Thus, the echocardiographic isovolumic index was defined as follows: IVI (%) = [(R-MVO − LVET)/LVET] × 100 = (IVT/LVET) × 100.

Recordings were made during quiet respiration and 5 suitable cycles were averaged to determine the isovolumic index. Because we did not calculate the delay in the carotid pulse tracing, the actual preejection period (time for electromechanical delay plus isovolumic contraction) and the precise duration of isovolumic relaxation could not be determined separately by this method.

The E point-septal separation was determined in all suitable M-mode recordings (51 of 55 patients) and considered abnormal when ≥5.5 mm.[16] PEP/LVET was calculated from the simultaneous electrocardiogram and micromanometer ascending aortic pressure tracing in the 6 patients studied at the time of catheterization.[17] The preejection period was measured from the onset of the Q wave to the onset of the most rapid upstroke of the ascending aortic pressure tracing. In 7 of the 12 patients with cardiomyopathy PEP/LVET was determined noninvasively in standard fashion[1–3] on the same day as the echocardiographic study.

High fidelity left ventricular pressure tracings were digitized at 200 samples/s and the first derivative of the left ventricular pressure was computed. End-diastolic pressure was defined as the pressure at which dP/dt reached 200 mm Hg/s and the pressure increased monotonically thereafter. The interval of isovolumic relaxation was defined from the time of peak negative dP/dt to a point at which the left ventricular pressure was at least 10 mm Hg above end-diastolic pressure of that beat. Left ventricular isovolumic pressure (P) with respect to time (t) was then fitted to an exponential curve[18] of the form: $P = P_0 \exp(-t/T)$, where P_0 is the pressure at peak negative dP/dt and T is the time constant. In each patient T was measured from the same 5 beats from which the isovolumic index was calculated. T_1[10] was calculated in the same fashion using only the first 40 ms of the isovolumic pressure decline.

Biplane left ventricular cineangiograms were examined independently by 2 observers without knowledge of the isovolumic index for identification of areas of hypokinesia, akinesia, or dyskinesia.

Gated equilibrium radionuclide angiograms at rest were obtained by a protocol validated in our laboratory and described previously.[19] The difference in counts/cycle in studies repeated at least 1 month apart was ±1% and the interobserver variation was also ±1% counts/cycle. The radionuclide ejection

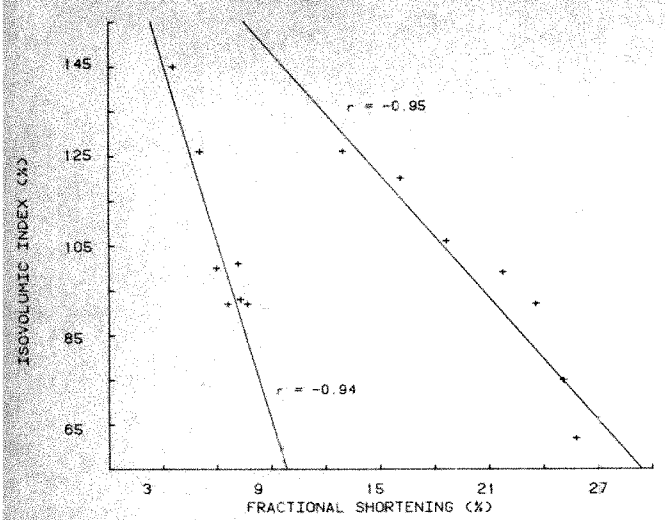

FIGURE 2. Correlation between fractional shortening and isovolumic index is demonstrated in 2 dogs.

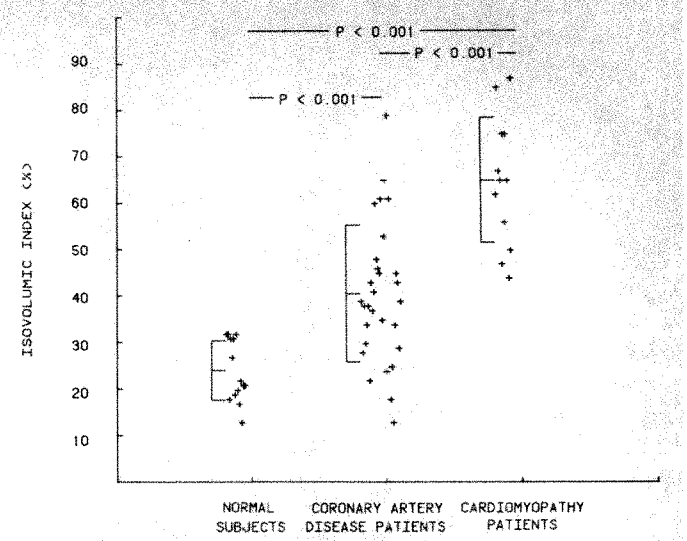

FIGURE 3. Isovolumic index in the study population. Means ± 1 standard deviation are shown.

fraction was determined without knowledge of the isovolumic index.

Statistics: All data are given as mean ± 1 standard deviation. The chi-square test with Yate's correction and the paired and unpaired Student's *t* tests were used when appropriate to assess statistical significance. Correlations were tested using linear regression analysis.

"Sensitivity" was defined as the number of true-positive test results divided by the total number of subjects with the clinical abnormality being analyzed. "Specificity" was defined as the number of true-negative test results divided by the total number of subjects without the clinical abnormality being analyzed. "Predictive accuracy" was defined as the number of true-positive test results divided by the total number of positive test results.

Results

Animal studies: Figure 2 demonstrates the correlations in 2 dogs between the isovolumic index and fractional shortening during 7 stepwise increases in the left ventricular filling pressure. Note that the isovolumic index decreased as fractional shortening improved. In 3 of the remaining 4 dogs, the correlations were also high ($r = -0.94$, -0.97, and -0.99), whereas the last correlation was -0.75.

Clinical studies: The isovolumic index did not correlate significantly with age, heart rate, systolic blood pressure, or mean blood pressure. As shown in Figure 3, normal subjects had the lowest isovolumic index (24 ± 7%) in contrast to patients with cardiomyopathy (65 ± 14%, $p < 0.001$ versus normal subjects) and those with coronary artery disease (40 ± 15%, $p < 0.001$ versus normal subjects and patients with cardiomyopathy).

All normal patients had an isovolumic index ≤32% whereas all patients with cardiomyopathy had values >32%. The coronary group showed some overlap with the normal subjects, but the majority (21 of 29, 72%) had an isovolumic index >32%.

Analysis of the coronary patients alone (Table I) showed no significant difference in the absolute value of the IVI in those who (1) were or were not taking beta-blocking drugs, (2) did or did not have a wall motion abnormality, (3) had a normal or reduced ejection fraction, and (4) had an elevated or normal left ventricular end-diastolic pressure.

Table II demonstrates the sensitivity, specificity, and predictive accuracy of an elevated isovolumic index (>32%) and an abnormal E point-septal separation (≥5.5 mm)[16] for (1) the presence of disease in the entire study group; (2) the presence of coronary disease (excluding coronary patients in the cardiomyopathy group); (3) the presence of wall motion abnormalities whether segmental or diffuse (including patients with cardiomyopathy); and (4) the presence of an abnormal ejection fraction. A radionuclide ejection fraction <50% or an angiographic ejection fraction <55% was consid-

TABLE I Subclassification of Patients With Coronary Artery Disease

Class	Patient Data	Isovolumic Index (%)	
I	On beta-blocking drugs (n = 18)	44 ± 15	
			p = NS
	Off beta-blocking drugs (n = 11)	35 ± 12	
II	Wall motion abnormality (n = 14)	43 ± 11	
			p = NS
	No wall motion abnormality (n = 7)	46 ± 19	
III	Subnormal ejection fraction (n = 10)	42 ± 12	
			p = NS
	Normal ejection fraction (n = 17)	40 ± 17	
IV	Left ventricular end-diastolic pressure >12 mm Hg (n = 9)	41 ± 11	
			p = NS
	Left ventricular end-diastolic pressure ≤12 mm Hg (n = 12)	47 ± 16	

ered abnormal. Note that the isovolumic index was a more sensitive indicator than an abnormal E point-septal separation for the presence of these commonly employed markers of left ventricular dysfunction. However, the specificity and predictive accuracy tended to be lower. Because the E point-septal separation was always normal when the isovolumic index was normal whereas the isovolumic index was sometimes increased despite a normal E point-septal separation, it follows that the sensitivity, specificity, and predictive accuracy of the presence of abnormalities of either of these measures or both merely reflected the behavior of the isovolumic index alone.

For purposes of comparison with E point-septal separation, an abnormal isovolumic index was defined as any value greater than the highest found in our normal group (that is, 32%), because this is the way an abnormal E point-septal separation has been defined previously.[16] Using >38% (2 standard deviations above the normal group mean) as the definition of an abnormal isovolumic index, the sensitivity decreased modestly. However, sensitivity improved when either or both of these measures were abnormal (Table III).

Simultaneous hemodynamic and echocardiographic data from the 6 coronary patients so studied are shown in Table IV. All patients had significant wall motion abnormalities. Despite the occurrence of both normal and abnormal ejection fractions and end-diastolic pressures and the wide range of peak positive and negative dP/dt values, all patients had abnormal time constants of relaxation.[9,10] Note that the isovolumic index was >38% in 5 of the 6 and >32% in all, whereas all had a normal PEP/LVET (<0.42).[20,21] In contrast, in the 7 patients with cardiomyopathy in whom these determinations were made, both PEP/LVET and the isovolumic index were abnormal.

As indicated, the PEP/LVET and the isovolumic index could be compared in a total of 13 patients (6 with coronary artery disease and 7 with cardiomyopathy). In this subgroup, the PEP/LVET (expressed as a percentage) averaged 45 ± 14 and was invariably smaller than the isovolumic index, which averaged 60 ± 17 ($p < 0.01$).

In a random subgroup of 10 patients the isovolumic index as measured independently by 2 observers varied by ±8%. In a separate subgroup of 7 subjects, the re-

TABLE II Sensitivity, Specificity, and Predictive Accuracy of an Increased Isovolumic Index (↑IVI) or Abnormal E Point-Septal Separation (↑EPSS) for the Presence of Disease and Left Ventricular Dysfunction

		Sensitivity	Specificity	Predictive Accuracy	Chi-Square*	p Value
Presence of disease	↑IVI	80% (33/41)	100% (14/14)	100% (33/33)	24.92	<0.001
	↑EPSS	54% (20/37)	100% (14/14)	100% (20/20)	10.29	<0.01
Presence of coronary disease (excluding patients with ischemic cardiomyopathy)	↑IVI	72% (21/29)	100% (14/14)	100% (21/21)	17.02	<0.001
	↑EPSS	32% (8/25)	100% (14/14)	100% (8/8)	3.84	<0.05
Abnormal rest ejection fraction	↑IVI	91% (20/22)	61% (19/31)	63% (20/32)	12.56	<0.001
	↑EPSS	74% (14/19)	80% (24/30)	70% (14/20)	11.74	<0.001
Segmental wall motion abnormality	↑IVI	86% (12/14)	76% (16/21)	71% (12/17)	10.53	<0.01
	↑EPSS	58% (7/12)	95% (19/20)	88% (7/8)	8.71	<0.01
Segmental or diffuse wall motion abnormality	↑IVI	92% (24/26)	76% (16/21)	83% (24/29)	20.26	<0.001
	↑EPSS	79% (19/24)	95% (19/20)	95% (19/20)	21.30	<0.001

By definition all normal patients had a normal IVI (≤32%). Numbers in parentheses refer to actual number of patients.
* Chi-square analysis with Yates' correction.

TABLE III Sensitivity, Specificity, and Predictive Accuracy of an Increased Isovolumic Index (↑IVI)* and an ↑IVI + Abnormal E Point-Septal Separation (↑EPSS) for the Presence of Disease and Left Ventricular Dysfunction

		Sensitivity	Specificity	Predictive Accuracy	Chi-Square†	p Value
Presence of disease	↑IVI	66% (27/41)	100% (14/14)	100% (27/27)	14.53	<0.001
	↑IVI + ↑EPSS	76% (31/41)	100% (14/14)	100% (31/31)	21.28	<0.001
Presence of coronary disease (excluding patients with ischemic cardiomyopathy)	↑IVI	52% (15/29)	100% (14/14)	100% (15/15)	8.96	<0.01
	↑IVI + ↑EPSS	66% (19/29)	100% (14/14)	100% (19/19)	13.88	<0.001
Abnormal rest ejection fraction	↑IVI	91% (20/22)	81% (25/31)	77% (20/26)	23.58	<0.001
	↑IVI + ↑EPSS	91% (20/22)	71% (22/31)	69% (20/29)	17.47	<0.001
Segmental wall motion abnormality	↑IVI	64% (9/14)	81% (17/21)	69% (9/13)	5.55	<0.02
	↑IVI + ↑EPSS	79% (11/14)	81% (17/21)	73% (11/15)	9.84	<0.01
Segmental or diffuse wall motion abnormality	↑IVI	77% (20/26)	81% (17/21)	83% (20/24)	12.27	<0.001
	↑IVI + ↑EPSS	88% (23/26)	81% (17/24)	85% (23/27)	20.15	<0.001

* Greater than 38% (that is, 2 standard deviations above the mean IVI of normal subjects).
† Chi-square analysis with Yates' correction. Number in parentheses refer to actual number of patients.

TABLE IV Simultaneous Hemodynamic and Echocardiographic Data in Subgroup of Patients With Coronary Artery Disease Studied With Micromanometer Tip High Fidelity Pressure Transducers

Ejection Fraction	Systolic Blood Pressure (mm Hg)	LVEDP (mm Hg)	Peak Positive dP/dt (mm Hg/s)	Peak Negative dP/dt (mm Hg/s)	T (ms)	T_1 (ms)	PEP/LVET	IVI (%)
0.57	130	9	1,630 ± 89	1,531 ± 66	57.2 ± 2.6	53.1 ± 6.5	0.38	48
0.50	165	25	1,508 ± 19	1,630 ± 130	54.5 ± 8.1	68.0 ± 3.0	0.24	46
0.53	130	7	1,529 ± 43	1,665 ± 154	50.5 ± 1.3	61.2 ± 1.6	0.38	45
0.52	170	13	1,638 ± 238	2,040 ± 250	53.3 ± 2.3	64.7 ± 8.8	0.26	61
0.70	160	11	1,426 ± 308	1,765 ± 213	50.1 ± 5.4	54.8 ± 9.9	0.28	34
0.48	120	15	1,213 ± 23	1,469 ± 55	51.5 ± 2.0	55.0 ± 1.7	0.35	53

Data are given as mean ± 1 standard deviation.
See text for definition of T and T_1.
IVI = isovolumic index; LVEDP = left ventricular end-diastolic pressure; LVET = left ventricular ejection time; PEP = preejection period.

producibility of the measurement from 2 different echocardiograms performed on 2 separate occasions (at least 24 hours apart) when there had been no interval change in clinical status or drug therapy was ±5%.

Discussion

The isovolumic index as we have defined it is an easily obtainable echocardiographic measurement that requires only the recording of an electrocardiographic R wave, a carotid arterial pulse tracing, and the echocardiogram of the anterior leaflet of the mitral valve. These recordings are well within the capabilities of any echocardiographic laboratory and do not require special equipment or a change in the usual routine of echocardiographic examination. Furthermore, the noninvasive nature of this procedure lends itself to widespread application and repeated measurements over the course of a patient's illness or perhaps during interventions and specific therapy.

Although the use of single-channel dual echocardiography allows for the direct measurement of isovolumic contraction and relaxation,[22] it is often difficult to obtain consistent, clear, simultaneous echograms of aortic and mitral valve opening and closure, and it is virtually impossible with only 1 operator. The isovolumic index can be recorded in virtually any patient and without the need for split-screen capabilities or added personnel.

The rationale for this measurement stems from 2 lines of reasoning. First, abnormalities of left ventricular relaxation have been noted in patients with coronary artery disease even in the absence of wall motion abnormalities, subnormal values for ejection fraction at rest, or acute ischemia.[5–7,9,10] These abnormalities have been detected by measurement of peak negative dP/dt or the time constant or isovolumic pressure decrease using invasive techniques, or both. Although the isovolumic index gives no information about the rate of pressure decrease during relaxation, an abnormally slow rate of decline can obviously influence the isovolumic index by increasing the total isovolumic period. Indeed, others have shown that the isovolumic relaxation period as measured echocardiographically or by apexcardiography is prolonged at rest in many patients with coronary artery disease when compared with normal subjects.[11–14,23]

The second line of reasoning providing a rationale for measurement of the isovolumic index stems from previous work describing systolic time intervals. Initial observations demonstrated that nonvalvular heart disease tended to lengthen the preejection period while the ejection time became shortened. The PEP/LVET ratio provided a useful index which correlated with cardiac output and stroke volume.[1–3] Others showed similar correlations of PEP/LVET with fractional shortening.[4] Stack et al[21,24] demonstrated its apparent utility in coronary disease. In addition, Lewis et al[25] demonstrated that the PEP/LVET ratio was somewhat sensitive to the presence of wall motion abnormalities in patients with coronary disease. Although their patients with wall motion disorders had statistically lower angiographic ejection fractions than did those without segmental abnormalities, the average ejection fraction in both groups remained normal. Even so, PEP/LVET was significantly greater in the presence of segmental contraction disorders.

On the basis of these observations, we hypothesized that an index combining isovolumic contraction, relaxation, and left ventricular ejection times might be a sensitive marker for the presence of cardiac disease. We also anticipated that abnormalities in such an index might occur in the absence of commonly accepted indicators of left ventricular dysfunction, because abnormalities in the components of this index have been noted even without the presence of wall motion abnormalities or a depressed ejection fraction. The results shown in Table II appear to bear out these predictions. Thus, the isovolumic index is a sensitive indicator of the presence of disease even in the absence of wall motion abnormalities or a depressed ejection fraction, or both, and it is more sensitive than increased E point-septal separation in this regard. Perhaps not surprisingly, the specificity and predictive accuracy of the isovolumic index for the presence of these abnormalities are less impressive than its sensitivity. This finding could reflect the possibility that very subtle aberrations of the relation between isovolumic contraction and relaxation and ejection may result from the presence of coronary artery

disease even when the disease is uncomplicated by abnormalities of left ventricular function detected by other techniques. The use of a higher value to define an abnormal isovolumic index (>38%) enhanced specificity. Furthermore, the sensitivities of the isovolumic index and abnormal E point-septal separation were each improved when either or both of these abnormalities were present (Table III). Although the isovolumic index is highly sensitive and compares favorably with E point-septal separation, the overlap between patients with coronary artery disease and normal subjects (Fig. 3) demonstrates that it does not completely identify all such patients. As indicated previously, although patients with coronary disease may have abnormalities of the components of the isovolumic index without other indicators of abnormal ventricular function, it is not always the case. Hence, some degree of overlap is to be anticipated, and like all other noninvasive indexes, the isovolumic index is not completely sensitive in this regard.

Although we initially hoped that the isovolumic index would correlate in a linear fashion with ejection fraction in the entire clinical population as it did with fractional shortening in the experimental animals, this did not turn out to be the case. Similar problems have been noted by some with respect to the use of PEP/LVET or E point-septal separation for the prediction of ejection fraction in coronary patients.[16,26–28] Nevertheless, our experimental preparation demonstrated a high negative correlation of the isovolumic index with improved fractional shortening when each dog was considered individually. This finding underscores 2 points. First, as the animal studies demonstrate, the isovolumic index may be influenced by differences in loading conditions, variables that were not manipulated in our clinical population and that require further investigation. Second, although we showed the usefulness of an isolated determination of the isovolumic index in the clinical subjects the animal data suggest that serial measurements in an individual during changes in clinical status or therapy or during acute interventions may also be a useful application.

Although modest, age-dependent prolongation of systolic time intervals and relaxation have been observed,[9,23,29] others have failed to confirm this finding.[13] We found no age-dependence of the isovolumic index either in the entire study group or within each group. Similarly, the isovolumic index did not appear to be related to heart rate within the range of our study (46 to 99 beats/min), although it might vary as a function of heart rate in individual subjects.

This study does not specifically compare the isovolumic index with PEP/LVET as a predictor of coronary disease, wall motion abnormalities, or reduced ejection fraction. However, although PEP/LVET was calculated in only a minority of our coronary patients, it is of note that in each of these cases the isovolumic index was abnormal despite the presence of a normal PEP/LVET. This finding is consistent with the work of several other investigators who have demonstrated that PEP/LVET is not always sensitive in patients with coronary disease and left ventricular dysfunction.[26–28]

It is important to stress certain methodologic features of measurement of the isovolumic index, particularly as they relate to comparisons between the isovolumic index and routinely obtained PEP/LVET ratios. We chose the peak of the R wave from which to measure the interval of total electromechanical systole and isovolumic relaxation (R-MVO) because in our experience it is more easily reproducible than the onset of the Q wave, particularly in tracings recorded on the echocardiographic strip chart. As a consequence, a substantial portion of the true electromechanical delay is not included in the R-MVO interval. In subjects with a normal PEP/LVET, the time for electromechanical delay accounts for a much greater portion of the PEP/LVET ratio than it does in individuals with an increased PEP/LVET, assuming a QRS complex of normal duration. This disproportionate contribution of electromechanical delay in normal compared with abnormal subjects is further exaggerated in determining the isovolumic index because of the addition in the numerator of the isovolumic relaxation time, which is also shorter in normal subjects. The standard technique for measuring PEP/LVET employs the onset of the Q wave as the beginning of PEP. If PEP/LVET were defined from the peak of the R wave, however, values for PEP/LVET in normal subjects would be systematically much shorter than those calculated in the usual fashion. This explains the fact that our isovolumic index value of 24 ± 7% in normal subjects apears surprisingly small in comparison with standard PEP/LVET ratios. Furthermore, in the abnormal subjects in whom PEP/LVET and the isovolumic index could be compared, the index was appropriately longer than PEP/LVET, as would be anticipated in a group in which electromechanical delay is a less important determinant of both ratios. Moreover, methodologic differences in the recording of timing intervals can also produce substantially different results.[3,15,21,23] It is therefore important to employ strict methodologic techniques in calculating the isovolumic index, particularly in timing the beginning of electromechanical systole and mitral valve opening.

We conclude that the isovolumic index is a sensitive indicator of left ventricular dysfunction and of the presence of coronary disease in some patients without abnormalities of other measures of systolic function. Furthermore, because the isovolumic index is easily determined during routine echocardiography, it may also be useful in serial measurements in individual patients during various phases of disease or therapy, an application that will require future validation.

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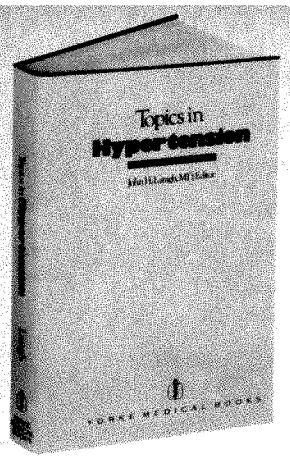

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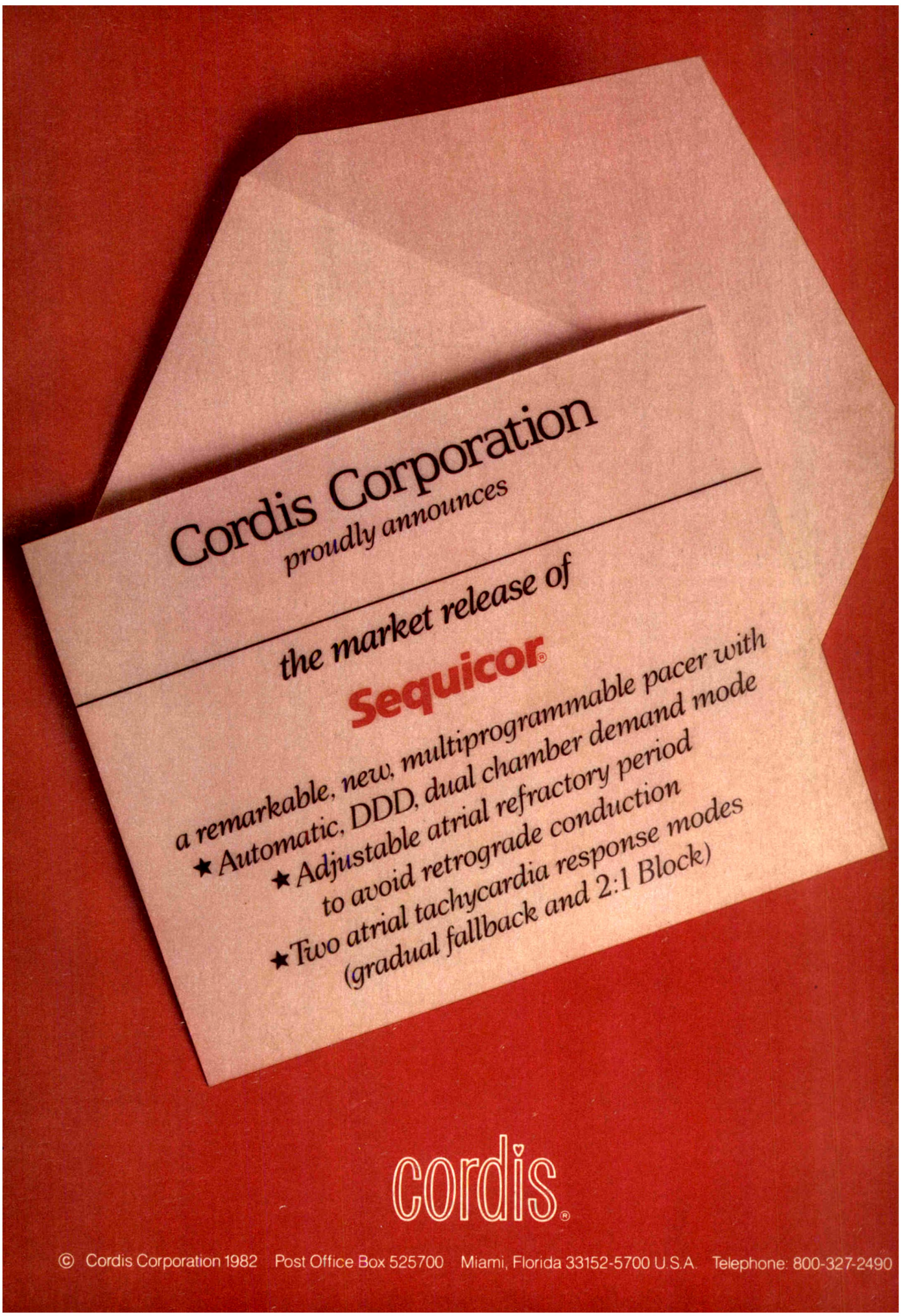
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Modes	DDD, DVI, DAD, VDD, VAT, VVI, DOO, VOO
Minimum Pacing Rate, (Interval)	50 (1200), 60 (1000), 70 (857), 80 (750)
Maximum Pacing Rate (Interval)	100 (600), 130 (461), 160 (375), 180 (333)
Atrial Sensitivity, (mV)	0.8, 1.5, 7.0, OFF
Ventricular Sensitivity, (mV)	0.8, 1.5, 2.5, OFF
Atrial Output Pulse Duration, (ms)	OFF, 0.5, 1.0, 1.5,
Ventricular Output Pulse Duration, (ms)	0.5, 1.0, 1.5, 2.0,
A/V Delay (ms)	80, 120, 165, 250
Atrial Tachycardia Response	Fall Back, 2:1 Block
Fall Back Rate (Interval)	55 (1.090), 65 (932), 75 (800), 85 (706)

Sequicor Refractory Periods

Atrial Tachycardia Response	Maximum Rate	Total Atrial Refractory	Total Ventricular Refractory	A/V Programmed Delay	Total Atrial Refractory Following the Ventricle Pulse
2:1 Block	100 ppm	600 ms	302 ms	80 ms	520 ms
				120	480
				165	435
				250	350
	130 ppm	461 ms	302 ms	80 ms	381 ms
				120	341
				165	296
				250	211
	160 ppm	375 ms	302 ms	80 ms	295 ms
				120	255
				165	210
				250	125
	180 ppm	333 ms	302 ms	80 ms	253 ms
				120	213
				165	168
				250	83
Any Fall Back Rate	Any Maximum Rate	305 ms	302 ms	80 ms	225 ms
				120	185
				165	140
				250	55

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The medical literature describes currently accepted indications for various pacing modes. The physician's clinical experience and judgment must ultimately be the guide in selecting the pacing mode best suited to the patient's needs. *The physician should be thoroughly familiar with the pacing mode chosen.*

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Warnings

None

Adverse Effects

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3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS

In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (eg, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS

Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (eg, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS

Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion, particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram, and clinical status of patient.

ADVERSE REACTIONS

Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION

Usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

C81-72 (1/25/82)

Consult complete product literature before prescribing. 128-3678-A

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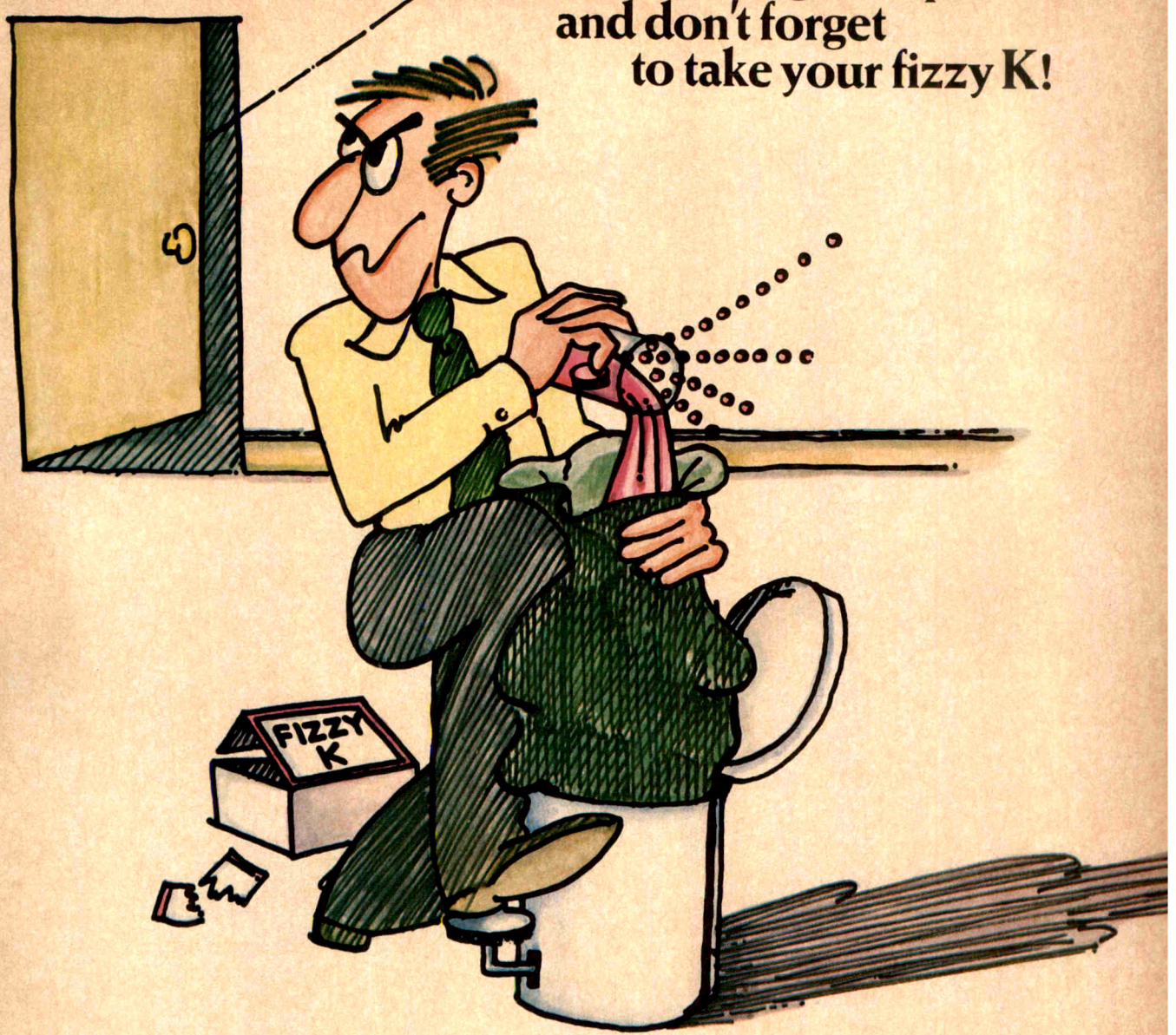
CIBA

Take out the garbage, Ralph– and don't forget to take your fizzy K!



In correcting diuretic-induced alkalosis

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☐ Nonchloride effervescent tablets, such as K-Lyte®, and nonchloride liquids, such as Kaon® elixir, fizzle out in correcting hypochloremic alkalosis.

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*Slow-release potassium chloride preparations should be reserved for patients who cannot tolerate, refuse to take or have compliance problems with liquid or effervescent potassium preparations, because of reports of intestinal and gastric ulceration and bleeding with slow-release KCl preparations.

Slow-K®

CIBA 165

potassium chloride slow-release tablets 8 mEq

Please see adjoining page for brief Prescribing Information.

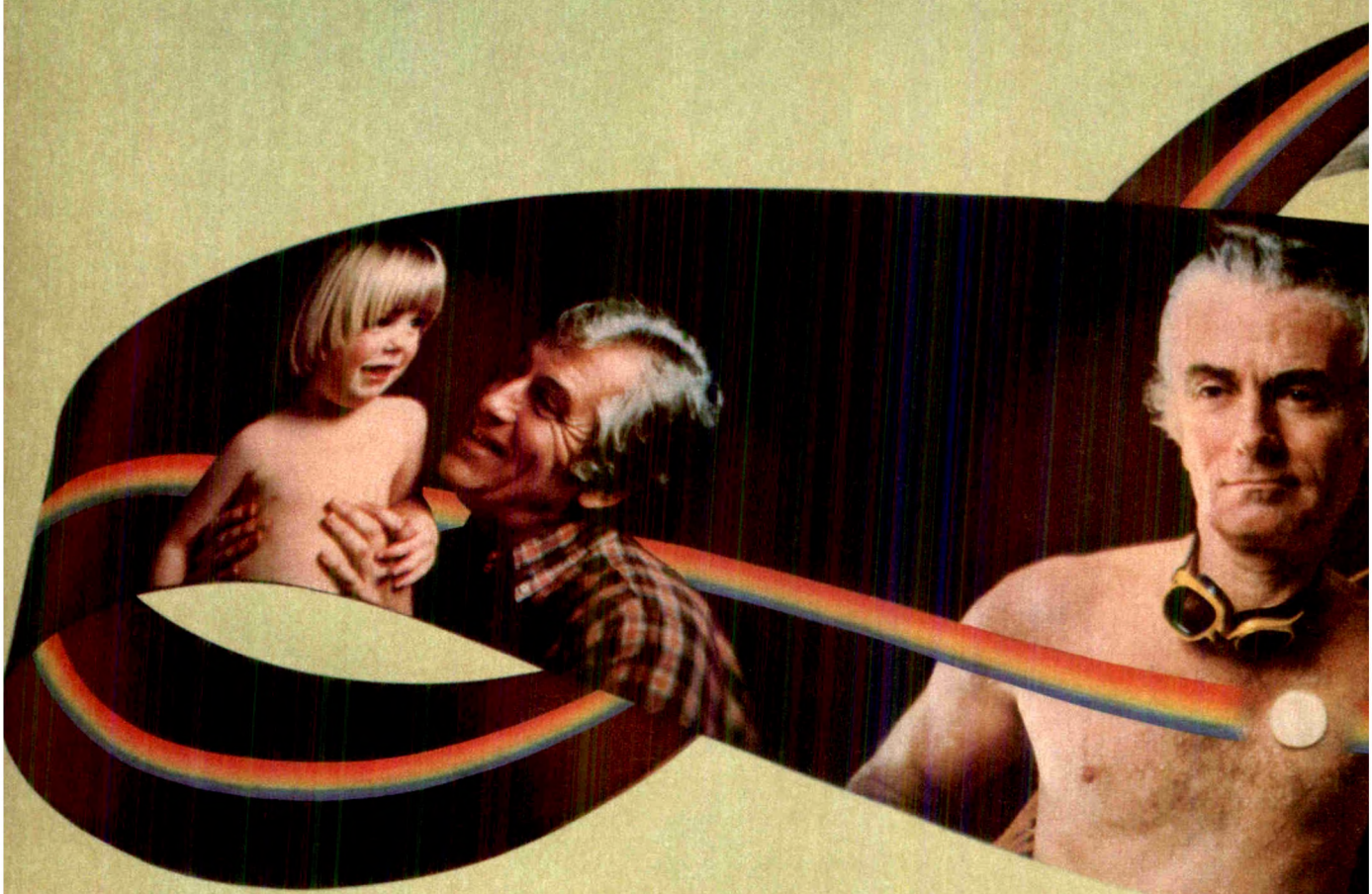
CIBA

A113

NITRODISC

(nitroglycerin) 5-MG/24-HR; 10-MG/24-HR PAD

Continuous anginal



Contraindications for nitroglycerin include patients with increased intraocular pressure. Side effects include headache, hypotension, flushing, and dizziness. In terminating treatment, both the dosage and frequency of application must be gradually reduced during a period of four to six weeks.

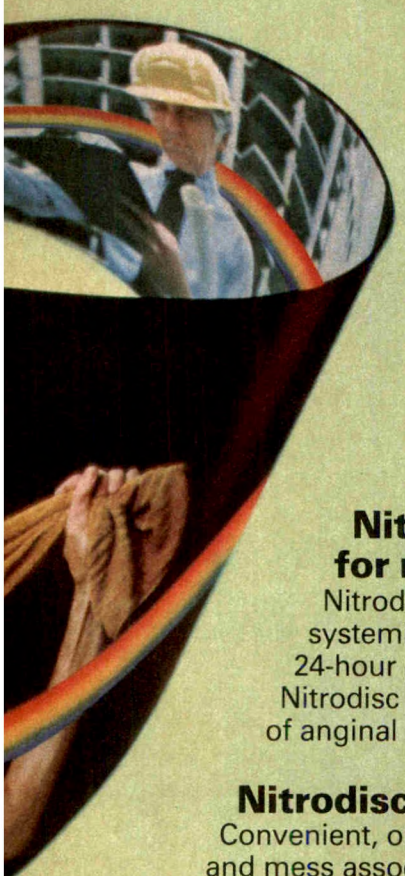
protection...q.d.

Preliminary results from a clinical study indicate 24-hour improvement in exercise capacity

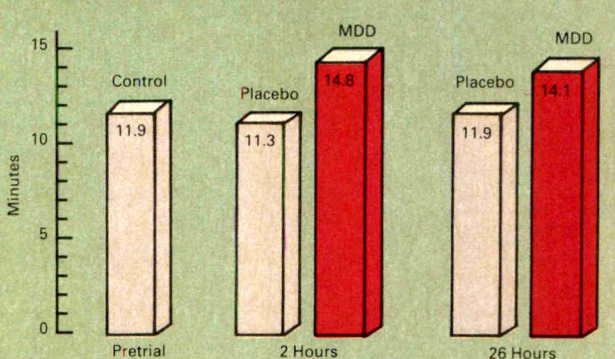
Until now, the clinically recognized benefits of a single nitrate dose have not been documented beyond 12 hours.

In a controlled study,[1] Searle's new nitroglycerin Microseal Drug Delivery™ (MDD) system provided an 18% average increase in exercise capacity 26 hours after application.[2]

In addition, the need for sublingual nitroglycerin was reduced.



Mean Exercise Duration



Nitrodisc (nitroglycerin) eliminates the need for multiple doses of long-acting oral nitrates

Nitrodisc's unique solid polymer releases nitroglycerin into the systemic circulation at a controlled and sustained rate over a 24-hour period.

Nitrodisc (nitroglycerin) is not intended for the immediate relief of anginal attacks.

Nitrodisc enhances compliance

Convenient, once-daily dosage schedule, plus the absence of bother and mess associated with nitroglycerin ointments.

Secure, waterproof adhesive allows for a complete range of daily activities.

1 The interim results presented include data on eight patients completing the protocol to date. A total of twenty patients will be included.

2 Thompson RH: Clinical use of transdermal delivery devices with nitroglycerin. Presented at the Medical Therapy for Angina in the 1980s: New Horizons Symposium, Atlanta, April 24, 1982.

In another clinical study conducted among cardiac rehabilitation participants, concomitant Nitrodisc (nitroglycerin) propranolol therapy did not demonstrate a significant improvement over propranolol alone.

Please see the following page for the complete prescribing information.

SEARLE

5-MG/24-HR; 10-MG/24-HR

NITRODISC™

(nitroglycerin)

DESCRIPTION: The Nitrodisc pad incorporates a patented Microseal Drug Delivery™ system consisting of a solid, nitroglycerin-impregnated polymer bonded to a flexible, non-sensitizing adhesive bandage. It is designed to be applied topically. Nitrodisc provides constant and controlled drug delivery over a uniform skin surface area for 24 hours.

Nitrodisc is available in two strengths that release either 5 mg or 10 mg of nitroglycerin during a 24-hour period. The 5 mg/24 hr system contains 16 mg nitroglycerin over an 8 cm^2 releasing surface. The 10 mg/24 hr system contains 32 mg nitroglycerin over a 16 cm^2 releasing surface (see HOW SUPPLIED section).

ACTIONS: When a Nitrodisc pad is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart and peripheral vasculature) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is due to a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In addition, a direct effect of nitroglycerin on the coronary vessels is recognized as well.

In clinical studies, transdermal absorption of nitroglycerin from Nitrodisc occurred in a continuous and well-controlled manner for a minimum of 24 hours. Therapeutic plasma levels were attained within 1 hour after the application of the pad and remained in the therapeutic range for 24 hours. Plasma levels of nitroglycerin were still detectable 30 minutes after removal of the system.

The amount of nitroglycerin released (5 mg/24 hr or 10 mg/24 hr) represents the mean absorption rates through skin determined during clinical evaluations. Absorption may vary among individuals.

INDICATIONS AND USAGE: Nitrodisc is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Nitrodisc (nitroglycerin) is contraindicated in patients known to be intolerant of organic nitrate drugs, and in patients with marked anemia, increased intraocular pressure, or increased intracranial pressure.

WARNINGS: In patients with acute myocardial infarction or congestive heart failure, Nitrodisc should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of patients with angina, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent potential withdrawal reactions, which are characteristic of all vasodilators in the nitrate class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness, or dizziness, particularly orthostatic hypotension, may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Nitrodisc is not intended for immediate relief of anginal attacks. For this purpose, occasional use of sublingual preparations may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Nitrodisc therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist, Nitrodisc (nitroglycerin) dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION: A Nitrodisc pad should be applied once each day. To use the pad, follow the instructions on the package. Nitrodisc should be applied to a skin site free of hair and not subject to excessive movement. It should not be applied to the distal parts of the extremities. A suitable area should be shaved free of hair, if necessary. The application site should be changed slightly each time to avoid undue skin irritation. A new pad should be applied if the product loosens.

The optimal dosage regimen should be selected based upon the clinical response, the side effects, and the effects of therapy upon blood pressure and heart rate. It is recommended that therapy be initiated with the smaller pad, and that the larger pad be utilized when a greater response is desired. In the event that higher doses are necessary, multiple pads may be applied.

PATIENT INSTRUCTIONS FOR APPLICATION: These are provided with the product.

HOW SUPPLIED:

Nitrodisc	5 mg/24 hr	10 mg/24 hr
Drug released per 24 hours	5 mg	10 mg
Total drug content	16 mg	32 mg
Drug releasing surface	8 cm^2	16 cm^2

Nitrodisc pads are supplied in cartons of 30. Store at a controlled room temperature of 59°-86°F (15°-30°C). **Do not refrigerate.** Extremes of temperature and humidity should be avoided.

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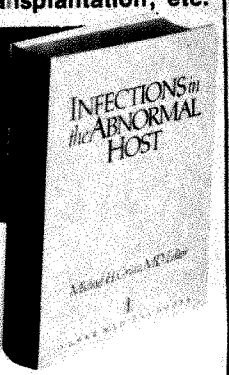
INFECTIONS
IN THE ABNORMAL HOST

Edited by Michael H. Grieco, M.D.
Text by 47 Specialists. Illustrated with 147 Drawings and Photos, 78 in Full Color



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Exercise-Induced Decrease in Flow Through Stenotic Coronary Arteries in the Dog

JEFFREY S. SCHWARTZ, MD, BRUCE TOCKMAN, BS, JAY N. COHN, MD, and ROBERT J. BACHE, MD

In the presence of a coronary stenosis, it is generally believed that exercise-induced ischemia is caused by an inadequate increase in coronary blood flow. This study was carried out to test the hypothesis that, in the presence of a critical coronary stenosis, exercise would result in a decrease in flow across the stenosis. Five dogs were chronically instrumented with a flow probe and a wire snare occluder on the circumflex coronary artery and with catheters in the left atrium, left ventricle, and aorta. Four dogs also had a catheter in the circumflex coronary artery distal to the occluder. Measurements were recorded with the animals resting quietly and then during moderate exercise.

In the absence of a stenosis, circumflex flow increased with exercise. In 13 experiments in which a severe stenosis was produced in the circumflex coronary artery, the changes from rest to exercise were as follows: heart rate from 102 ± 7 to 151 ± 12 beats/min ($p < 0.001$), mean aortic pressure from 103 ± 4 to 107 ± 3 mm Hg (difference not significant), distal circumflex pressure from 71 ± 5 to 36 ± 2 mm Hg ($p < 0.001$), the pressure gradient across the stenosis from 32 ± 4 to 71 ± 3 mm Hg ($p < 0.001$), stenosis resistance from 2.3 ± 0.7 to 13.9 ± 3.9 units ($p < 0.01$), and flow through the stenotic artery from 29 ± 4 to 10 ± 3 ml/min ($p < 0.001$). Left ventricular filling pressure increased from 9 ± 1 to 15 ± 1 mm Hg ($p < 0.01$). The decrease in intraluminal pressure distal to the stenosis and thus in the stenosis itself may have resulted in passive narrowing of the stenotic segment, which may have caused the decrease in flow. Exercise, therefore, may result in a decrease in flow through a stenotic coronary artery.

It is generally believed that in patients with occlusive coronary artery disease, exercise results in an attenuated increase in flow through stenotic coronary arteries. Ischemia consequently develops because flow cannot increase sufficiently to meet myocardial oxygen demands. In support of this concept, studies of exercise in the presence of experimental coronary stenoses have shown an increase in total flow through the stenotic artery although the increase in flow was less than that through normal arteries.[1]

From the Department of Medicine, Cardiovascular Division, University of Minnesota Medical School, Minneapolis, Minnesota. This study was supported by Young Investigator Research Award Grant HL-21298 and by Grant HL-20598 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, and by a Grant-in-Aid from the American Heart Association, Dallas, Texas, with funds contributed in part by the American Heart Association, Minnesota Affiliate, Minneapolis, Minnesota. Manuscript received April 13, 1982, accepted June 9, 1982.

Address for reprints: Jeffrey S. Schwartz, MD, Department of Medicine, Box 258, Mayo Memorial Building, University of Minnesota Hospitals, Minneapolis, Minnesota 55455.

Previous studies in open-chest dogs have shown that in the presence of a severe nonfixed coronary stenosis, vasodilation of the distal coronary bed caused by transient coronary occlusion,[2,3] injection of contrast medium,[2] or rapid ventricular pacing[4] was associated with an increase in stenosis resistance and a decrease in flow through the stenotic artery.

Exercise is also known to cause vasodilation of the distal coronary bed and might also be expected to result in a similar decrease in flow through a severely stenotic coronary artery. However, there are potentially important differences between exercise-induced distal bed dilation and the previously studied interventions which might affect flow through a stenotic artery. As opposed to transient coronary occlusion, injection of contrast medium, or rapid pacing, exercise may cause an increase in systemic arterial pressure and may alter autonomic tone. Furthermore, the previous studies were all acute preparations in anesthetized open-chest dogs while exercise studies would necessitate intact unanesthetized chronically instrumented dogs. Therefore, the present

study was done to evaluate the effect of exercise on blood flow through severely stenotic coronary arteries.

Methods

We studied 5 chronically instrumented dogs weighing from 22 to 31 kg (mean 26 ± 2). The dogs were anesthetized with pentobarbital (25 mg/kg) and a left thoracotomy was performed in the fourth intercostal space. Heparin-filled catheters were placed in the aorta by way of the internal thoracic artery and in the left atrium and the left ventricle. The proximal portion of the left circumflex coronary artery was dissected free and a 2.5 or 3.0 mm electromagnetic flow probe was placed around the artery. A snare occluder was placed distal to the flow probe on the circumflex coronary artery. This occluder consisted of a soft wire snare threaded through polyethylene tubing. We were careful to be certain that the snare was placed loosely around the artery during surgery and that it had minimal contact with the artery before the chest was closed. In this way we hoped to minimize the development of fibrosis in the area where the stenosis would later be produced. A catheter was placed into the circumflex artery distal to the snare for the measurement of distal coronary arterial pressure. This catheter consisted of a short section of silastic tubing with an internal diameter of 0.02 in cemented to a long section of silastic tubing with an internal diameter of 0.04 in. A guidewire was inserted into the tubing to make it more rigid and the narrower section of tubing was threaded through a small branch of the circumflex artery into the left circumflex artery. The guidewire was then removed and the catheter was filled with heparin. The ends of the catheters, the snare, and the flow probe tubing were tunneled into a subcutaneous pouch and the chest was closed.

The studies were performed 1 to 2 weeks after surgery when the animals had recovered. Under 2% lidocaine infiltration anesthesia, the ends of the catheters and occluder tubing were removed from the subcutaneous pouch. The pressure catheters were connected to P23ID pressure transducers that were attached to a nylon vest which the dog had been trained to wear. In 1 dog, the distal catheter did not function so that resistance could not be calculated. In another dog the left ventricular catheter did not function. In the latter dog, however, left atrial pressure was measured so that left ventricular filling pressure could be determined. The end of the wire snare occluder was attached to a machinist's micrometer so that precise adjustments of the severity of the stenosis could be made. The micrometer was also mounted on the side of the nylon vest. The end of the flow probe was connected to a Statham P2202 electromagnetic flow meter. Zero flow, obtained by transient complete occlusion of the appropriate coronary artery, was determined frequently during the course of each experiment.

When the pressure and flow systems were functioning properly, the animal was allowed to rest quietly while a stenosis was produced in the coronary artery by tightening the wire snare. The animal then performed exercise, consisting of walking rapidly about the laboratory. Pressure and flow measurements were recorded during exercise. If exercise resulted in an increase in flow through the stenotic artery, the dog was again allowed to rest quietly while the snare was

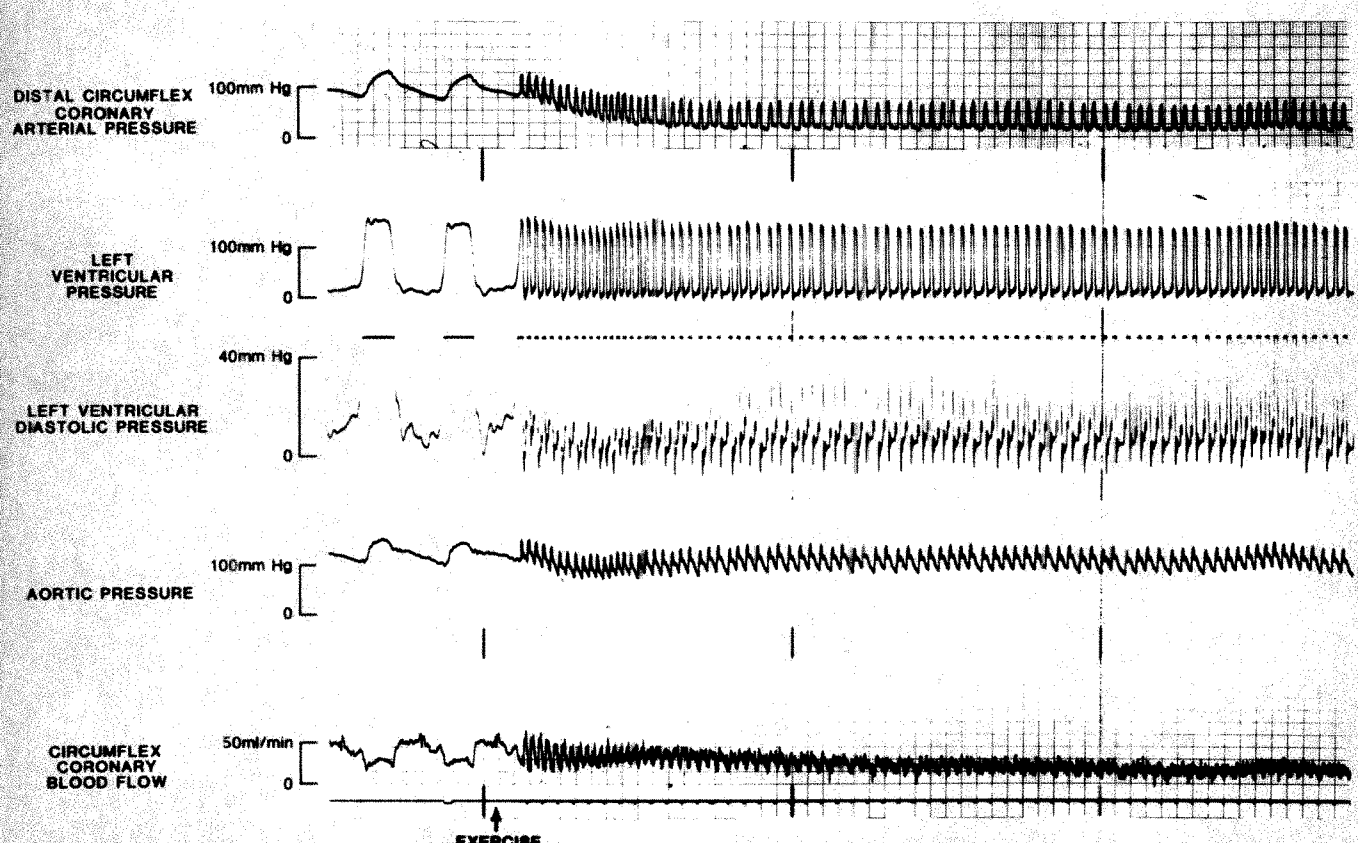

FIGURE 1. Effects of exercise in the presence of a severe circumflex coronary stenosis. Exercise resulted in a decrease in distal circumflex pressure and a decrease in flow through the stenotic circumflex artery. Each **short vertical line** at the bottom of the figure represents 1 second.

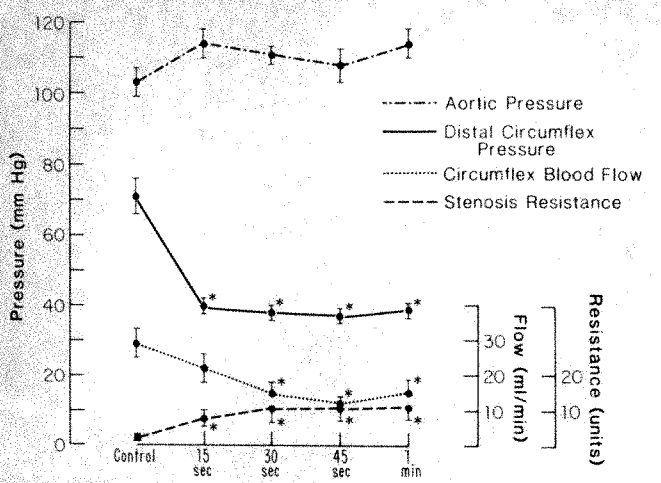

FIGURE 2. Mean hemodynamic changes during the first minute of exercise in the presence of a critical circumflex coronary stenosis. The **asterisks** indicate significant difference from control values ($p < 0.025$).

tightened further. Exercise was again performed. This was repeated until a degree of stenosis was reached at which exercise resulted in a decrease in flow through the stenotic artery.

All measurements were recorded on a Hewlett-Packard 7758B recorder at a paper speed of 1 to 50 mm/s. Mean resistance across the stenosis was expressed in resistance units (mm Hg/ml/min) and was calculated using the formula R = (P1-P2)/Q, where P1 = mean pressure in the ascending aorta, P2 = mean coronary pressure distal to the stenosis, and Q = mean circumflex coronary blood flow. All data are shown as mean values ± standard error of the mean. Significance of the differences was determined by Student's *t* test for paired data and analysis of variance.[5]

Results

In the absence of a coronary stenosis, exercise caused a consistent increase in blood flow through the circumflex coronary artery. As a stenosis was produced and made more severe, there was less of a flow increase in response to exercise. When the stenosis was very severe, in 14 experiments in 5 dogs, exercise was associated with an actual decrease in flow through the stenotic coronary artery. The decrease in coronary flow with exercise was reproducible in 4 of the 5 dogs. In each of these dogs, whenever a sufficiently severe stenosis was produced, exercise resulted in a decrease in coronary flow. In 3 of the dogs, 3 separate experiments were done in which flow decreased in the presence of a critical stenosis; in the fourth dog, 4 such experiments were done.

Figure 1 shows a tracing from 1 of the experiments in which a critical circumflex stenosis was present. Exercise resulted in a decrease in distal coronary pressure and a decrease in flow through the stenotic artery.

Figure 2 shows the mean hemodynamic changes during the first minute of exercise in those experiments in which a critical circumflex stenosis was present. Aortic pressure did not change significantly. Distal circumflex pressure fell within the first 15 seconds and did not change significantly thereafter. Stenosis resistance increased within the first 15 seconds of exercise after which it did not change significantly. Flow began to decrease during the first 15 seconds of exercise. However, this decrease did not reach statistical significance until 30 seconds after the onset of exercise. There was no further change in flow during the remainder of the first minute of exercise.

Table I shows the peak hemodynamic effects of exercise in the experiments in which a critical coronary stenosis was present. Exercise resulted in an increase in heart rate from 102 ± 7 to 151 ± 12 beats/min. There was no significant change in aortic pressure. Distal circumflex pressure fell with exercise, the pressure gradient across the stenosis increased, and stenosis resistance increased markedly. Flow through the stenotic artery fell from 29 ± 4 to 10 ± 3 ml/min. Left ventricular filling pressure increased from 9 ± 1 to 15 ± 1 mm Hg.

A decrease in flow through a stenotic artery with exercise occurred in this study only when the stenoses were sufficiently severe to result in a modest decrease in blood flow through the stenotic arteries during quiet resting conditions. Thus, in the presence of the stenoses but before exercise, flow was 78 ± 3% of the control pre-stenosis flow.

Discussion

The decrease in flow with exercise was associated with a marked increase in stenosis resistance. Calculated hydraulic resistance may vary even for a stenosis that is thought to be anatomically fixed. It has previously been shown that as flow across a stenosis increases, calculated resistance increases because the pressure gradient increases proportionally more than flow.[6,7] However, in this study the increase in resistance across the stenosis with exercise was associated with a decrease in flow, making flow changes alone an unlikely expla-

TABLE I Peak Hemodynamic Response to Exercise in the Presence of a Severe Circumflex Stenosis

	Aortic Pressure (mm Hg)	Distal Circumflex Pressure (mm Hg)	Stenosis Pressure Gradient (mm Hg)	Circumflex Blood Flow (ml/min)	Stenosis Resistance (mm Hg/ml/min)	Left Ventricular Filling Pressure (mm Hg)	Heart Rate (beats/min)
Control	103 ± 4	71 ± 5	32 ± 4	29 ± 4	2.3 ± 0.7	9 ± 1	102 ± 7
Exercise	107 ± 3	36 ± 2	71 ± 3	10 ± 3	13.9 ± 3.9	15 ± 1	151 ± 12
	NS	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.01$	$p < 0.01$	$p < 0.001$

NS = not significant.

nation for the increase in stenosis resistance and suggesting that a true increase in stenosis severity occurred.

We did not attempt to calculate distal coronary arteriolar resistance in this study. Recent experiments have suggested that the resistance to flow in the distal coronary bed may be best evaluated in terms of the slope of coronary pressure-flow curves and the pressure at which flow stops.[8–10] Resistance calculations using the quotient of distal coronary pressure and flow may not be accurate. Since we did not attempt to evaluate pressure-flow curves, we could not accurately evaluate distal coronary resistance. However, the marked fall in distal coronary pressure during exercise suggests that the distal coronary arteriolar bed did dilate. This finding, in combination with the marked increase in stenosis resistance during exercise, suggests that the decrease in flow during exercise was due to an increase in the severity of the stenosis.

There are 3 possible mechanisms for the increased severity of the stenosis during exercise. The first is active constriction of the artery in the area of the stenosis. Exercise causes increased sympathetic outflow which may cause active constriction of the stenotic segment. It has previously been shown that sympathetic stimulation can decrease the diameter of large coronary arteries.[11] Although active constriction of a section of artery which is externally compressed with a snare seems unlikely, we cannot definitely exclude this possibility as a cause of the increased stenosis resistance and decrease in flow.

The second possible explanation for the increase in stenosis resistance and fall in flow is passive narrowing of the stenotic segment. It has previously been shown that the resistance of a nonfixed coronary stenosis passively changes in response to alterations in intraluminal pressure, increasing with a fall in intraluminal pressure and decreasing with a rise in intraluminal pressure.[6,12] Stenoses produced with external snares are capable of similar passive changes in resistance.[13] In the present study, exercise resulted in a marked fall in distal coronary pressure. Pressure in the stenotic segment should be as low as or lower than pressure distal to the stenosis.[14] The fall in intraluminal pressure distal to the stenosis and thus in the stenotic segment itself may have resulted in a passive decrease in the diameter of the stenotic segment. This passive narrowing of the stenosis would then result in the observed increase in stenosis resistance and the decrease in flow through the stenotic artery. Even small changes in the diameter of a severe arterial stenosis can have marked effects on flow through the stenosis.[6]

Santamore and Walinsky[15] studied isolated perfused carotid arteries in which a stenosis was produced with an external snare. The perfusion apparatus was constructed so that peripheral resistance distal to the stenosis could be decreased. These authors found that a decrease in resistance distal to the stenosis caused a decrease in stenosis diameter, as determined by radiographic analysis, and an increase in stenosis resistance. These data support the concept that the increase in stenosis resistance and fall in flow which occur in response to dilation of the distal coronary bed are due, at least in part, to passive narrowing of the stenotic segment. In the present study, in which dilation of the distal coronary bed was induced by exercise, it seems probable that a similar mechanism was responsible for the increase in stenosis resistance and the decrease in flow—namely, a decrease in intraluminal pressure in the stenotic segment resulting in a passive decrease in stenosis diameter.

A third possible cause for the decrease in flow with exercise should be mentioned. During exercise fully developed turbulence may appear in the stenotic segment. Gould[7] has suggested that when turbulence develops fully, the loss of potential energy may be so great that aortic pressure would be inadequate to maintain flow, which could then decrease without a change in stenosis diameter. Since we did not directly demonstrate a change in stenosis diameter during exercise in this study, we cannot exclude the possibility that the development of turbulence may have contributed to our findings.

The decrease in flow through the stenotic artery with exercise was associated with a modest rise in left ventricular filling pressure, suggesting that ischemia may have occurred and may have been causing regional left ventricular dysfunction. We did not attempt to continue our hemodynamic observations after cessation of exercise because of concern that the low flow through the coronary artery, which was associated with an increase in left ventricular filling pressure, might result in the animal's death. Instead, the coronary stenosis was released immediately after exercise.

The decrease in flow through the stenotic artery occurred in response to a relatively low level of exercise. We initially planned to have the animals exercise maximally on a treadmill, but this became unnecessary when we found that flow through a severely stenotic artery decreased in response to a relatively mild degree of exercise.

An increase in severity of coronary stenoses during exercise has been demonstrated clinically and has been attributed to exercise-induced coronary spasm.[16–18] It is always difficult to extrapolate from the results of animal experiments to the clinical situation. However, in the present study, when the stenosis was critically severe, exercise reproducibly resulted in a fall in flow through the stenotic artery. Although we cannot definitely exclude the possibility that the spasm played a role in our findings, it seems unlikely that spasm would reproducibly occur in response to exercise in the presence of severe stenoses and not occur in the presence of mild or moderate stenoses.

In summary, this study has shown that exercise may cause an increase in the resistance of severe nonfixed coronary stenoses and a decrease in flow through the stenotic artery. These findings suggest that in the presence of a severe, nonfixed coronary stenosis, exercise-induced myocardial ischemia may be caused by a combination of increased myocardial oxygen demand and decreased supply.

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Ventricular Fibrillation Resulting From Ischemia at a Site Remote From Previous Myocardial Infarction

A Conscious Canine Model of Sudden Coronary Death

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In anesthetized dogs, a 30 gauge silver wire was inserted into the lumen of the left circumflex (LC) coronary artery and myocardial ischemic injury was produced by subsequent occlusion of the left anterior descending (LAD) coronary artery for 90 minutes followed by reperfusion through a critical stenosis. Four days after acute myocardial infarction, with the dog ambulatory, the intimal surface of the LC coronary artery was injured by applying a 150 μA anodal current. Coronary artery thrombosis and subsequent reduction in coronary artery blood flow were accompanied by S-T segment changes at 132 ± 65 minutes (mean ± standard deviation [SD]) with ventricular fibrillation (VF) occurring in 29 of 30 dogs (97%) at 141 ± 60 minutes. Infarct mass in the LAD distribution was 15 ± 8% of total left ventricular mass with no histochemical evidence of irreversible ischemic injury in the LC coronary artery distribution. VF was preceded by the development of delayed electrical activity within the LC coronary artery distribution, and the development of ventricular arrhythmias accompanied by continuous local electrical activity within the subepicardial region of the distribution of the LC coronary artery. In 10 dogs with placement of a critical stenosis around the LAD coronary artery without earlier occlusion and reperfusion, LC intimal injury and subsequent thrombus formation resulted in only 2 deaths (20%) from VF. Thus, acute myocardial ischemia at a site distant to a previous myocardial infarction enhances the likelihood of primary VF in the conscious dog. This model of sudden coronary death may simulate the clinical state in man and might serve as an appropriate model for the study of electrophysiologic mechanisms associated with the development of VF and for the evaluation of potential antifibrillatory drugs.

Recent studies by Schuster and Bulkley[1] demonstrated that acute occlusion of 1 coronary artery could lead to ischemia in the myocardium supplied by a second coronary artery, if the second vessel was critically narrowed and dependent on collateral blood flow from the first coronary artery. These investigators referred to this phenomenon as "ischemia at a distant site," which could contribute to postinfarction angina pectoris and sudden coronary death, an event almost always due to unexpected ventricular tachyarrhythmias.[2,3] The high rate of recurrence of ventricular fibrillation (VF) and sudden coronary death in patients rescued from a previous event is well documented[2,4,5] and suggests that the superimposition of an ischemic episode on an already jeopardized myocardium could lead to an arrhythmia terminating in VF.

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There is an urgent need for the development of pharmacologic interventions capable of preventing VF and sudden coronary death in patients identified as being at high risk. One major deficiency in this field of investigation is the lack of a suitable animal model that would permit preclinical studies to identify potentially useful therapeutic agents. Our results support the hypothesis that ischemia at a distant site (circumflex region) in a previously injured myocardium may serve as an important mechanism for the development of ventricular arrhythmias which terminate in sudden and unexpected VF. The experimental model described in this investigation is subject to ventricular tachyarrhythmias in response to programmed electrical stimulation and develops VF in the presence of regional ischemia. Therefore, the model affords the opportunity to initiate meaningful studies aimed at identifying antifibrillatory agents intended to prevent sudden coronary death in man.

Methods

Surgical Preparation of Dogs With Ischemic Myocardial Injury

Male mongrel dogs (14.6 to 25.6 kg) were anesthetized with pentobarbital sodium (30 mg/kg intravenously) and placed

on positive-pressure respiration using a volume-cycled Harvard pump. Aseptic surgical technique was employed for the insertion of cannulas in the jugular vein and carotid artery, both of which were exteriorized at the back of the neck.

The heart was exposed through a left thoracotomy in the fourth intercostal space. Both the left anterior descending (LAD) and the left circumflex (LC) coronary arteries were freed from the underlying myocardium at a distance of 0.5 to 1.0 cm from their origin. A 30 gauge Teflon®-coated silver wire, with 3 mm of the tip of a 25 gauge hypodermic needle secured on the wire's lead end to aid in penetration of the artery wall, was inserted through the wall of the LC coronary artery so that approximately 2 to 3 mm of the bare wire-needle tip assembly was within the vessel lumen and in contact with the intimal lining. The wire was secured to the epicardium with 2 sutures. The distal end of the silver wire was exteriorized at the back of the neck and would subsequently serve to deliver an anodal current of 150 μA to produce an electrolytic lesion on the intimal surface of the LC coronary artery. A Grass disk electrode was sutured to the subcutaneous tissue and completed the electrical circuit which consisted of a 9 V battery and a 250,000 Ω potentiometer placed in a series so as to allow control of the current output at the anode. The procedure was detailed by us in an earlier report.[6] In 6 of the animals, a calibrated electromagnetic flow probe was placed on the circumflex coronary artery proximal to the point of insertion of the silver wire electrode. The needle-wire assembly was inserted parallel to the inner surface of the LC coronary artery and in the absence of direct flow of current did not result in altered coronary artery blood flow, thrombus formation, or irreversible myocardial ischemic injury in the region of the distribution of the LC coronary vessel, even when left in place for 30 days.[6]

Ischemic myocardial injury was produced in the distribution of the LAD coronary artery as previously described.[7] This procedure involves the placement of a critical stenosis on the LAD coronary artery by adjusting a ligature tied around the artery and an 18 or 19 gauge needle. The needle is withdrawn and a determination made of the reactive hyperemic response to a 10 second occlusion of the LAD vessel. The constricting ligature is adjusted to reduce the reactive hyperemic response by at least 60%, but without reducing resting LAD coronary artery blood flow as recorded by an electromagnetic flow probe placed proximal to the point of vessel constriction. Once partial constriction is established, a Silastic® ligature (Retract-O-Tape®) is placed distal to the point of constriction and the LAD coronary artery is occluded for 90 minutes followed by reperfusion in the presence of the critical stenosis. The importance of the critical stenosis has been described previously by us[7] as well as by Sheehan and Epstein[8]: it reduces the incidence of VF and the development of hemorrhagic infarct on subsequent reperfusion of the myocardium in the distribution of the LAD coronary artery.

A bipolar plunge electrode consisting of a 25 gauge insulated stainless steel wire, 4 mm in length and separated by 2 mm, was placed in the ventricular septum adjacent to the right ventricular outflow tract. The electrodes were situated 1 cm from the medial border of the cyanotic area which appeared on occlusion of the LAD coronary artery. Silver disk electrodes were implanted subcutaneously for recording the electrocardiogram (lead II). The surgical incisions were closed, and the animals were given 6 mg/kg of ampicillin intramuscularly and permitted to recover from anesthesia. Figure 1 is a schematic representation of the surgical preparation of the canine heart in which the area supplied by the LAD coronary artery was subjected to ischemic injury by temporary coronary artery occlusion and reperfusion in the presence of a critical stenosis. In addition, a silver wire electrode was inserted in the LC coronary artery and will be used subsequently to induce an electrolytic lesion on the inner surface of the vessel. The bipolar electrode is to be used for programmed electrical stimulation of the heart and the induction of ventricular arrhythmias.

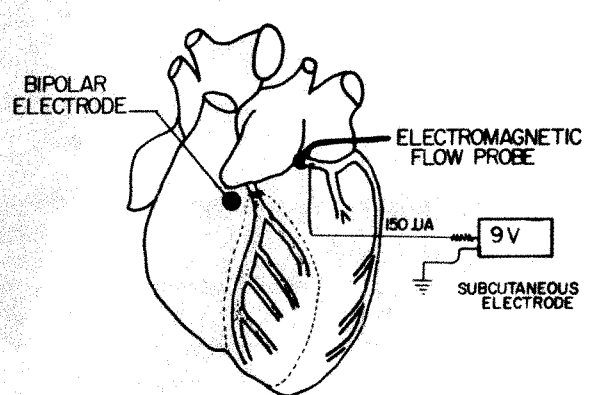

FIGURE 1. Schematic representation of canine heart in which a silver wire electrode is inserted into the LC coronary artery and is attached to the positive pole of a 9 V nickel-cadmium battery and a variable resistor which permits the current flow to be adjusted to 150 μA. The negative electrode is attached to the subcutaneous tissue. An electromagnetic flow probe is placed proximal to the intracoronary electrode. The LAD coronary artery has a critical stenosis in its proximal region, is occluded for 90 minutes, and then is reperfused in the presence of the critical stenosis which remains in place until completion of the study. A bipolar electrode in the interventricular septum is used to carry out programmed electrical stimulation after recovery from the operation. Control operated dogs were prepared in a similar manner but did not undergo occlusion of the LAD coronary artery (noninfarct group).

Experimental Procedures

Programmed electrical stimulation: The animals were returned to the laboratory after fully recovering from the operation and studied while conscious, unsedated, and resting comfortably in a sling. One, 2, and 3 ventricular premature stimuli (4 ms duration square-wave pulses, twice diastolic threshold) were applied to the interventricular septum at sequentially decreasing 10 ms intervals for S_2, S_3, and S_4 stimuli delivered from a Grass S-88 stimulator and SIU-5 stimulus isolation unit as described previously.[9,10] The ventricular stimuli from the stimulator were triggered from the R wave of the lead II electrocardiogram.

The procedure for programmed electrical stimulation can be summarized as follows: (1) Single premature ventricular stimuli (S_2) at twice diastolic threshold are introduced during normal sinus rhythm at decreasing 10 ms intervals from 350 ms until ventricular refractoriness occurs. (2) Double premature ventricular stimuli at twice diastolic threshold (S_2,S_3) are introduced during normal sinus rhythm at decreasing 10 ms intervals for S_2 stimuli from 350 ms until ventricular refractoriness occurs with S_2 to S_3 intervals of 200, 180, 170, 160, 150, 145, 135, and 130 ms. (3) Triple premature ventricular stimuli at twice diastolic threshold (S_2,S_3,S_4) are introduced during normal sinus rhythm at decreasing 10 ms intervals for S_2 stimuli from 350 ms until ventricular refractoriness occurs with S_2 to S_3 and S_3 to S_4 intervals as just stated. (4) Programmed electrical stimulation as just listed is performed during atrial pacing at rates up to 210 beats/min. (5) Intermittent ventricular pacing at rates up to 360 beats/min is performed.

The stimulation protocol was continued until reproducible sustained ventricular tachycardia could be obtained a mini-

mum of 3 times in each dog. No attempt was made to go beyond this end-point to circumvent the possible initiation of VF.

Initiation of LC coronary artery intimal injury and coronary artery thrombosis: On completion of the programmed electrical stimulation studies, the animals were placed in a quiet laboratory environment and monitored for aberrant electrocardiographic rhythms. The lead II electrocardiogram was transmitted through telemetry and stored on FM magnetic tape for subsequent analysis. Thus, the animals were studied while conscious, ambulatory, and in normal sinus rhythm. The telemetry transmitter and the 9 V battery source and variable resistor were carried in the pocket of a nylon vest (Alice King Chatham). In 6 animals in which electromagnetic blood flow probes were placed on the LC coronary artery, the study had to be conducted while the conscious, unsedated animals were maintained in a sling, thus limiting their range of movement.

Once adequate baseline recordings were obtained, a continuous direct current anodal current of 150 μA was applied to the intimal surface of the LC coronary artery. Previous unpublished studies demonstrated that an anodal current of 150 μA would reproducibly lead to oscillatory changes in the LC coronary artery blood flow within 60 to 90 minutes and that an occlusive thrombus would form within 120 to 180 minutes after initiation of current flow. An observer continuously monitored the transmitted data to detect changes in cardiac rhythm, S-T segment shifts, and LC coronary artery blood flow.

Noninfarcted control dogs with LAD coronary artery stenosis and subsequent LC coronary thrombosis: In 10 dogs that served as controls, the LAD coronary artery was constricted so as to minimize or abolish the reactive hyperemic response to a 10 second occlusion of the vessel. Unlike the previous animals in the experimental infarct group, the controls did not undergo temporary occlusion and reperfusion of the LAD coronary artery. Thus, myocardial tissue in the distribution of the vessel was not subjected to ischemic injury. As with the experimental infarct group, however, the control noninfarcted animals were subjected to electrically induced injury to the intimal surface of the LC coronary artery with subsequent formation of an occlusive thrombus and regional myocardial ischemic injury in the distribution of the occluded LC vessel.

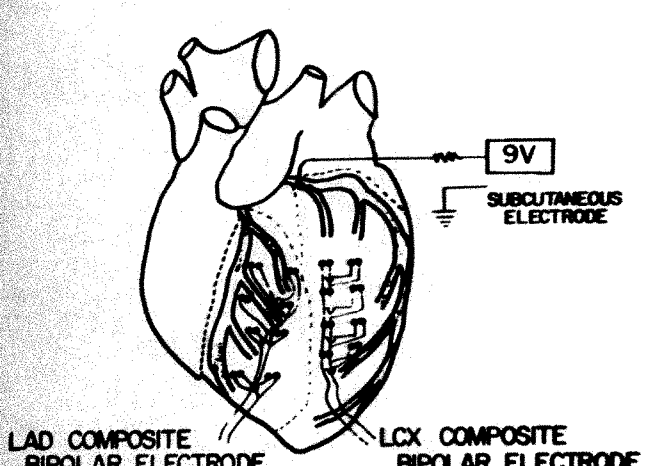

FIGURE 2. Schematic representation of the canine heart similar to that shown in Figure 1, illustrating placement of the bipolar composite electrodes used to record separate subepicardial electrograms from the region of the LAD and the left circumflex (LCX) coronary artery, so that regional electrical events in response to LC coronary artery thrombosis could be studied in the anesthetized open chest dog.

Electrophysiologic studies in the anesthetized dog: Male mongrel dogs were prepared in a manner identical to that described for the experimental group (n = 7) and for the control noninfarcted group (n = 6). The animals were returned to the laboratory 4 days after having undergone LAD coronary artery occlusion and reperfusion in the presence of a critical stenosis. The dogs were anesthetized and placed on positive-pressure respiration and the thoracotomy incision was reopened and the heart suspended in a pericardial cradle.

Sixteen pairs of insulated bipolar electrodes (0.05 mm in diameter, Teflon®-coated silver wire with 2 mm of exposed tip) were placed subepicardially in the region of distribution of both the LAD and LC coronary arteries (3 × 5 cm). Subepicardial bipolar composite recordings were obtained by summing the 16 bipolar electrode pairs so that separate recordings of composite electrograms could be obtained from each of the regions subserved by the LAD and LC coronary arteries (Fig. 2). The composite electrograms were filtered at 50 and 500 Hz. The electrograms were stored on FM magnetic tape and later recorded on a Visicorder (Honeywell model 1858) along with the lead II electrocardiogram.

Control subepicardial bipolar composite electrode recordings were obtained after which the LC coronary artery was subjected to a continuous 150 μA direct current. Measurements of the delay in the subepicardial electrograms were made on a storage oscilloscope (Tektronix model 5111). We quantitated the degree of delay and fragmentation in the subepicardial zone during the induction of thrombus formation and ischemia in the region of distribution of the LC coronary artery by measuring the maximal delay between the Q wave of the lead II electrogram and the last distinct and sharply defined activity in the subepicardial composite electrogram during normal sinus complexes. The studies were terminated 8 hours from the start of LC coronary artery simulation or on development of VF.

Quantitation of the extent of irreversible ischemic myocardial injury: At the conclusion of each experiment the heart was removed, examined, and prepared for histochemical staining to identify irreversibly damaged myocardium. The LC coronary artery was examined for thrombus adherent to the site of intimal injury or in the distal branches of the vessel. The heart was sectioned transversely, apex to base, into 5 mm thick sections which were incubated at 39°C in a 0.5% solution of triphenyltetrazolium hydrochloride in 0.01 *M* phosphate buffer at pH 7.4. The histochemical stain is reduced in the presence of dehydrogenase enzyme activity, thus rendering viable myocardial tissue an intense "brick-red" color and clearly demarcating irreversibly injured tissue which retains a pale coloration. Recent studies[11] confirm that failure of myocardial tissue to reduce triphenyltetrazolium correlates with the presence of irreversibly injured myocardium and agrees with previous observations from our laboratory.[7]

In the control animals and in the groups used for electrophysiologic studies, thioflavin-S (10 ml of a 5% solution) was injected into the left atrial appendage just before sacrifice by the electrical induction of VF. The heart was removed, sectioned, and stained as described previously. The sections were viewed under ultraviolet light to determine the pattern of distribution of the thioflavin-S which is a flow-dependent fluorescent stain. The appearance of the stain in the region of distribution of the LAD coronary artery was used to confirm the patency of the vessel in which a critical stenosis had been established 4 days earlier. After being viewed under ultraviolet light the ventricular sections were stained in triphenyltetrazolium chloride as described herein.

Statistics: Values for the data are presented as mean ±

standard deviation. Fisher's exact test was used to analyze the differences in survival between operated control animals and those with experimental infarct. A 2-way analysis of variance was used to analyze for differences in the means between the experimental and the control groups.

Results

Programmed electrical stimulation in the conscious dog with experimentally induced myocardial infarction (LAD coronary artery occlusion and reperfusion): Thirty dogs were subjected to temporary occlusion of the LAD coronary artery and reperfusion in the presence of a critical stenosis, and after full recovery from the operation, the animals were evaluated for the presence of myocardial electrical instability using programmed electrical stimulation. Single, double, and triple premature ventricular stimuli were introduced into the ventricular septum as described previously. Myocardial electrical instability as revealed by electrically inducible ventricular arrhythmias was manifest as either nonsustained ventricular tachycardia in 16 dogs (53%), sustained ventricular tachycardia in 7 dogs (23%), or VF in 4 dogs (13%). Of the 30 animals evaluated on the fourth day after myocardial infarction, 27 (90%) had electrically inducible ventricular arrhythmias in response to programmed cardiac stimulation. The results obtained with programmed electrical stimulation are summarized in Table I and a representative experiment showing the induction of a nonsustained ventricular tachycardia is presented in Figure 3 (top panel). Induced sustained ventricular tachycardia was terminated by rapid ventricular pacing. Once repeatedly initiated nonsustained ventricular tachycardia had been observed in a given animal, using 1 or more modes of atrial or ventricular stimulation, we did not attempt more aggressive stimulation using closer ventricular coupling intervals or faster rates of ventricular pacing so as to avoid excess attrition of animals because of electrically induced VF. In the 4 dogs in which VF developed during programmed electrical stimulation, resuscitation was successfully achieved by transthoracic direct current shock.

TABLE I Incidence of Myocardial Electrical Instability on Day 4 After Myocardial Infarction

	LAD Coronary Artery Infarct Group (n = 30)		Control Group (n = 10)	
	n	%	n	%
Not inducible	3	10	10	100
Nonsustained VT	16	53	...	...
Sustained VT	7	23	...	...
VF	4*	13	...	...

* Defibrillated using transthoracic direct current cardioversion (200 to 250 W-s). VT = ventricular tachycardia.

Programmed electrical stimulation in the conscious dog with an LAD coronary artery critical stenosis, but without myocardial ischemic injury (control, noninfarct group): Programmed electrical stimulation was performed in 10 conscious dogs on the fourth day after placement of a critical stenosis in the LAD coronary artery, but in which myocardial tissue was not subjected to a period of ischemia leading to irreversible injury. Neither nonsustained nor sustained ventricular tachyarrhythmia could be induced in any of the animals through the use of programmed electrical stimulation. Thus, observations in the 10 animals without previously induced ischemic myocardial injury contrast with those obtained in animals that had been subjected to LAD coronary artery occlusion and reperfusion in which myocardial electrical instability could be demonstrated 4 days later in 27 of 30 dogs undergoing provocative electrical stimulation of the heart.

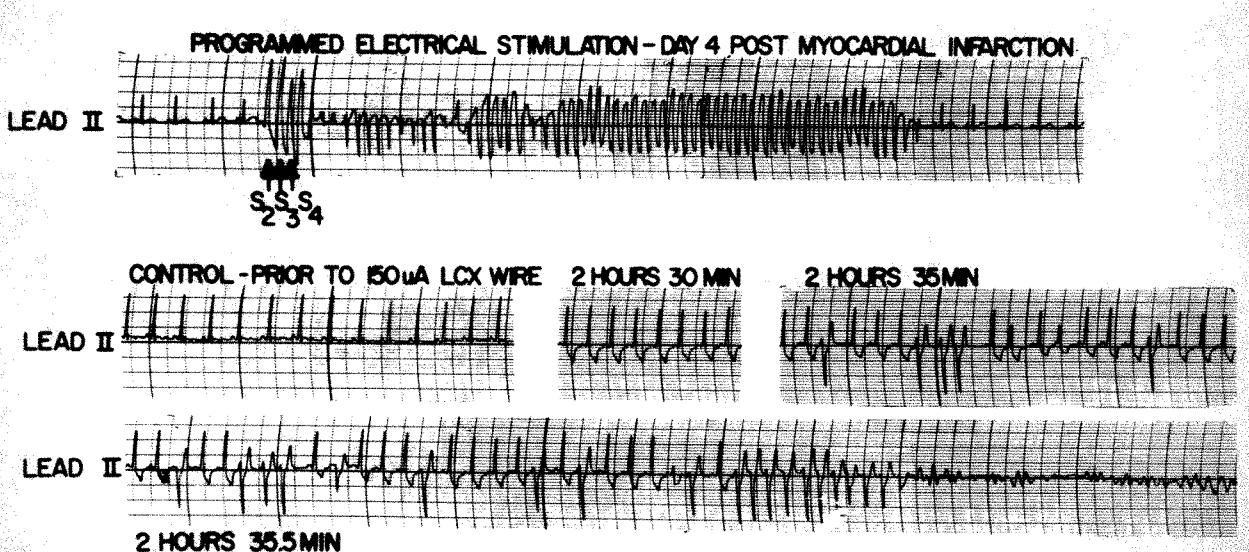

FIGURE 3. Ventricular fibrillation in the conscious dog. On day 4 after myocardial infarction, 3 premature ventricular stimuli at twice diastolic threshold are applied to the interventricular septum (coupling intervals of 180, 150, and 150 ms) **(upper panel)**. A polymorphic nonsustained ventricular tachycardia is produced. Lead II electrocardiograms before and after stimulation of the intimal surface of the left circumflex (LCX) coronary artery **(lower panels)** show the development of S-T segment depression followed by disturbances in cardiac rhythm. At 2 hours and 35.5 minutes, the ventricular rhythm degrades to VF.

TABLE II **Time Course for the Development of Electrocardiographic Changes in the Conscious Dog in Response LC Coronary Artery Thrombosis**

4 Days After MI	LAD Coronary Artery Infarct Group (n = 30)	Control Noninfarct Group (n = 10)
Minutes to S-T segment change	132 ± 65	133 ± 70
Minutes to premature ventricular contractions	136 ± 68	218 ± 192
Minutes to ventricular tachycardia	138 ± 58	280 ± 190
Minutes to VT or VF	141 ± 60	420
VF	29 (97%)	2 (20%)

No significant differences between groups. MI = myocardial infarction.

Ischemia at a distance (circumflex region) in the dog previously subjected to myocardial ischemic injury and (LAD region) reperfusion: On completion of the protocol for programmed electrical stimulation the animals in both the infarct group (n = 30) and the control noninfarct group (n = 10) were subjected to direct anodal current of 150 μA applied to the intimal surface of the LC coronary artery through the previously implanted silver wire electrode. The animals were conscious and either unrestrained or limited in mobility by being placed in a sling. As we demonstrated previously,[6,12–14] electrically induced lesions on the intimal surface of the LC coronary artery result in platelet aggregation and transient oscillation in coronary blood flow associated with changes in the S-T segment,[14] suggesting subendocardial or transmural ischemia.

Continuous monitoring of the lead II electrocardiogram in each of the 30 animals during LC coronary artery stimulation showed that the mean time to initial S-T segment changes (>0.3 mV) was 132 ± 65 minutes, with some animals showing S-T segment depression (n = 25) and others manifesting ischemia by developing S-T segment elevation (n = 5). Premature ventricular beats were observed initially at a mean time of 136 ± 68 minutes after initiation of current flow to the LC coronary artery with the development of VF at 141 ± 60 minutes in 29 of 30 animals (97%) with chronic myocardial infarction due to LAD coronary artery occlusion and reperfusion in the presence of a critical stenosis (Table II). All animals were in normal sinus rhythm before the initiation of LC coronary artery stimulation and the development of S-T segment changes in the lead II electrocardiogram. The mean heart rate was 128 ± 19 beats/min. With the development of S-T segment alterations and presumably ischemia due to changes in LC coronary artery blood flow, the sinus rate increased to 169 ± 26 beats/min ($p < 0.05$). Premature ventricular beats or ventricular tachyarrhythmias were not considered in all instances as premonitory signs of VF. In 5 animals, VF was the initial electrocardiographic disturbance associated with the development of S-T segment changes, so that the fatal rhythm developed in the absence of a warning arrhythmia. Figure 3 is taken from a series of electrocardiographic recordings from 1 dog in which nonsustained ventricular tachycardia developed in response to programmed electrical stimulation when tested 4 days after LAD coronary artery occlusion and reperfusion. Subsequent anodal current injury in the LC coronary artery resulted in progressive changes in the electrocardiogram which first showed S-T segment depression and eventually culminated in VF. The time from the first appearance of changes in the S-T segment until the onset of VF showed wide variation among the 30 animals studied. In 6 animals the elapsed time between these events was <15 seconds.

In 6 conscious animals, continuous recordings were made of the lead II electrocardiogram, arterial blood pressure, and LC coronary artery blood flow during the induction of low amperage electrical stimulation to the intimal surface of the LC vessel. The initial LC coronary artery blood flow was 40 ± 8 ml/min and the mean arterial blood pressure averaged 101 ± 9 mm Hg. LC coronary blood flow was reduced to 4 ± 6 ml/min ($p < 0.01$) and was accompanied by S-T segment changes >0.3 mV with the maximal change occurring at 114 ± 59 minutes after initiating intimal stimulation of the coronary artery. Mean arterial blood pressure was reduced to 87 ± 9 mm Hg ($p < 0.05$). VF developed in each of the 6 animals within 131 ± 60 minutes from the induction of LC coronary artery stimulation. Figure 4 is a representative tracing from 1 of the conscious animals showing the sequence of changes in blood pressure, LC coronary blood flow, and the lead II electrocardiogram during the development of an ischemic episode in the distribution of the LC coronary artery which terminated in VF. In this particular experiment, there was an abrupt cessation of LC coronary artery blood flow, S-T segment depression appeared, and within 15 minutes VF developed.

During these studies the induction of intimal injury to the LC coronary artery was associated with marked alterations in coronary artery blood flow as recorded with an electromagnetic flow probe. Figure 5 is a representative tracing in which arterial blood pressure, the lead II electrocardiogram, and phasic and mean LC coronary artery blood flow are recorded from a conscious dog before and after initiation of current flow to the vessel wall. There is a gradual decrease in amplitude of the phasic coronary blood flow tracing without a change in the mean LC coronary artery blood flow. This is followed by the spontaneous development of a marked reactive hyperemic response (second panel, 1 hour, 9 minutes). Within 10 minutes after the previous record, there is a repetition of the event in which the phasic flow responses are attenuated only to be followed by a reactive hyperemic response. These coronary blood flow changes are cyclic until at 2 hours after the initiation of anodal stimulation of the vessel, coronary flow in the circumflex decreased to 0 and remained at this level until the fibrillation occurred shortly thereafter. Marked disturbances in the electrocardiogram occurred whenever the phasic flow response was attenuated and especially during the development of the reactive hyperemic response. In some instances, VF developed during the active arrhythmic phase associated with the

FIGURE 4. Ventricular fibrillation resulting from thrombotic coronary artery occlusion. Arterial pressure tracings, a lead II electrocardiogram, and left circumflex (LCX) coronary blood flow (mean and phasic) are shown before (control) and after stimulation of the intimal surface of the LC coronary artery. At 2.5 hours, S-T segment depression is present in the lead II electrocardiogram and LC coronary artery flow is 0 ml/min. Fifteen minutes later, sustained VF is observed. An occlusive thrombus, weighing 18 mg, was removed from the LC coronary artery at autopsy.

reactive hyperemic response and could account for our inability to identify occlusive thrombi in all animals dying suddenly as a result of VF.

Electrical induction of LC coronary artery thrombosis in the conscious dog with LAD coronary artery stenosis: Ten dogs serving as controls underwent stenosis of the LAD coronary artery, but were not subjected to occlusion and reperfusion. On the fourth postoperative day, a 150 μA anodal current was applied to the intimal surface of the LC coronary artery while the animals were conscious and ambulatory. Changes in the S-T segment, either elevation or depression, occurred at 133 ± 70 minutes and this value did not differ significantly from that seen in the previous group with chronic myocardial infarction (Table II). The onset of ventricular ectopic beats and the development of ventricular tachyarrhythmia in response to ischemia in the distribution of the LC coronary artery were delayed in the control group compared with the experimental animals with previous LAD coronary artery occlusion and reperfusion. Although 97% of the animals with previous myocardial injury developed VF in response to ischemic changes due to alterations in circumflex coronary artery blood flow, only 20% of the control animals ($p < 0.004$) died suddenly as a result of acute ischemia in the distribution of the LC coronary artery. Data for both the experimental infarct group and the control, noninfarct animals are presented in Table II.

Electrophysiologic studies in the anesthetized dog with previous LAD coronary artery occlusion

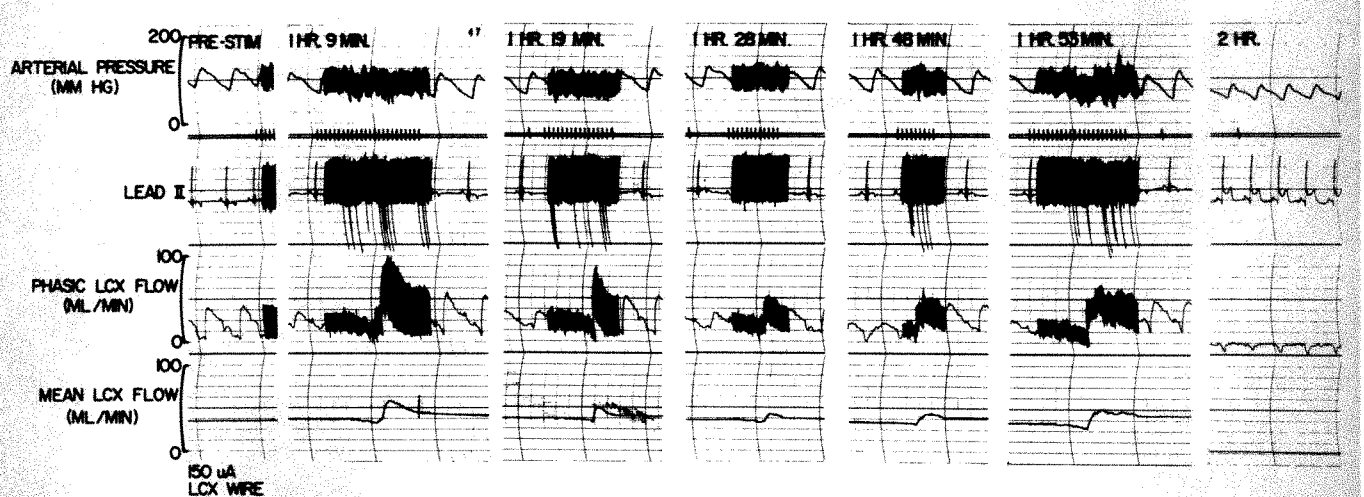

FIGURE 5. Representative recordings of arterial blood pressure, lead II electrocardiogram, and phasic and mean left circumflex (LCX) coronary artery blood flow from a conscious dog that had undergone LAD coronary artery occlusion and reperfusion in the presence of a critical stenosis. The **first panel on the left** is a control tracing. Subsequent recordings were made after the initiation of LC coronary artery stimulation with a 150 μA direct anodal current. See text for description.

and reperfusion and in control animals without chronic myocardial infarction: The need to obtain electrocardiographic recordings from the subepicardial region of the heart made it necessary to study animals in the anesthetized state and with the heart exposed. Seven dogs with chronic myocardial infarction due to previous LAD occlusion and reperfusion in the presence of a critical stenosis and 6 control dogs with LAD coronary artery stenosis but without chronic myocardial infarction comprised the study groups. Both groups were subjected to intravascular injury in the circumflex coronary artery by application of a 150 μA current while subepicardial bipolar composite electrograms were recorded from the respective areas of distribution of the LAD and LC coronary arteries. Recordings of the lead II electrocardiogram and the 2 sets of subepicardial bipolar electrograms were stored on FM magnetic tape and played back on a Honeywell Visicorder. After the control data were obtained, a 150 μA anodal current was applied to the LC coronary artery.

Figure 6 is a representative experiment showing the lead II electrocardiogram and separate subepicardial composite electrode recordings from the regions of distribution of the LAD and LC coronary arteries. Composite bipolar electrograms from the LAD and LC coronary artery distributions show discrete deflections without evidence of conduction delay or fragmentation of the normally conducted beats (upper left panel). Despite a region of chronic myocardial injury in the distribution of the LAD artery, there is no evidence of continuous electrical activity during electrical diastole from the subepicardial bipolar composite electrode overlying the area of chronic injury. With the appearance of S-T segment elevation in the lead II electrocardiogram (upper right panel), there is a progressive increase in conduction delay and fragmentation and a decrease in voltage amplitude and appearance of continuous diastolic electrical activity in the composite electrogram recording from the LC coronary artery distribution, whereas the composite bipolar recordings from the region supplied by the LAD coronary artery continue to show a uniform pattern of activation and become disorganized only when there is further disorganization of ventricular electrical activity in the limb lead electrocardiogram. The results in each of the animals with previous LAD coronary artery occlusion and reperfusion and subsequent acute ischemia in the region of the LC coronary artery were similar to those discussed herein (Table III). It was obvious that subepicardial delay of normally conducted beats and persistent diastolic activation developed initially in the region of myocardium supplied by the LC coronary artery and

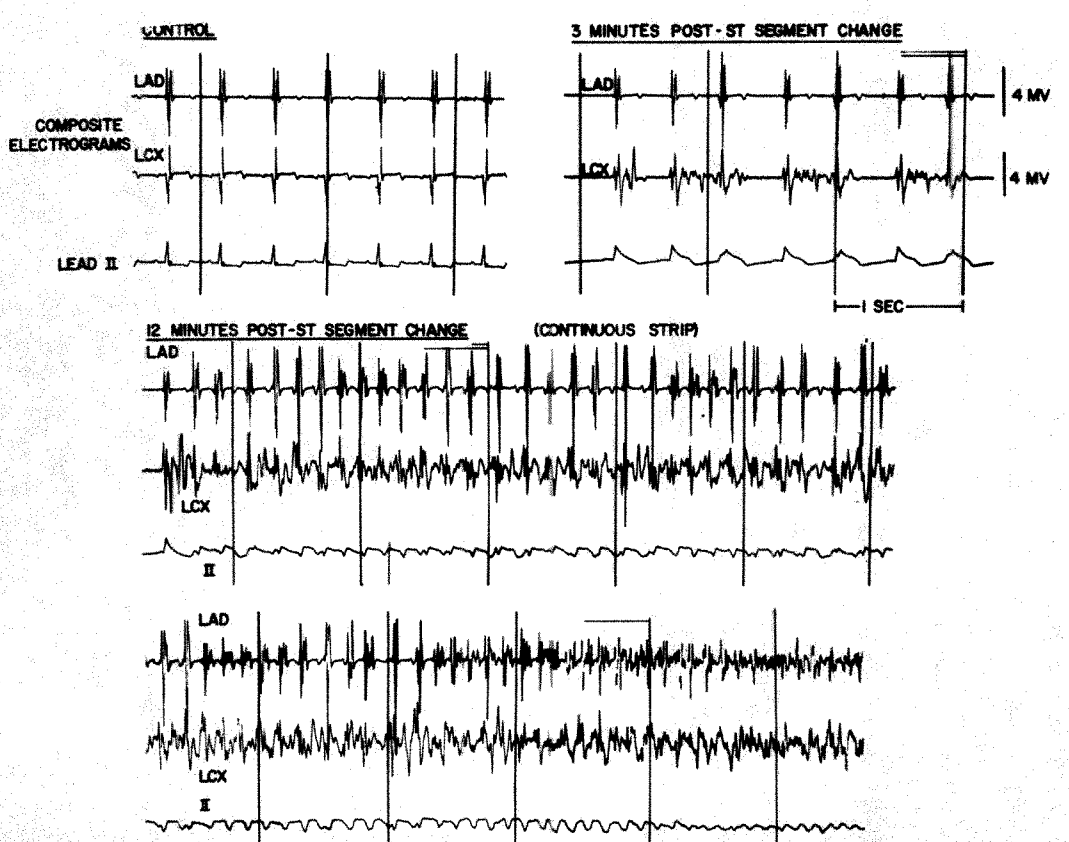

FIGURE 6. Canine model of sudden coronary death.[2] Control electrograms from the LAD and left circumflex (LCX) distributions are shown in conjunction with a lead II electrocardiogram. Three minutes after S-T segment elevation, delayed and fractionated electrical activity appeared in the circumflex distribution, spanning diastole and producing premature ventricular beats. Twelve minutes after development of S-T segment elevation, a sustained ventricular tachycardia leading to VF was present. Continuous electrical activation within the LC distribution was present from the initiation of tachycardia to VF.

TABLE III **Electrocardiographic Changes in the Anesthetized Canine During Induction of LC Coronary Artery Thrombosis**

4 Days After MI	LAD Coronary Infarct Group (n = 7)	Control Noninfarct Group (n = 10)
Minutes to S-T segment change	98 ± 58	122 ± 38
Minutes to premature ventricular beats	108 ± 55	128 ± 62
Minutes to VT	109 ± 54	196 ± 80
Minutes to VF	113 ± 55	126 (n = 1)

No significant differences between day 4 postinfarct group and control group. MI = myocardial infarction; VT = ventricular tachycardia.

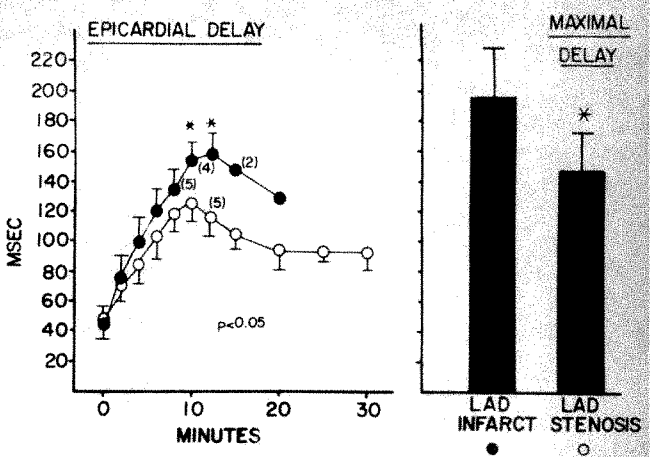

FIGURE 7. Epicardial delays (mean ± standard deviation) as recorded from the myocardial region supplied by the LC coronary artery in dogs that underwent occlusion and reperfusion of the LAD coronary artery (LAD infarct, n = 7) and in a group of dogs without ischemic injury but with a critical stenosis on the LAD coronary artery (LAD stenosis, n = 6). Myocardial activation time in each group before the development of myocardial ischemia was <60 ms. The presence of S-T segment changes was accompanied by the development of delayed electrical activation within the LC coronary artery distribution. Delay at 10 and 12 minutes after S-T segment changes was significantly greater in the LAD infarct group. The maximally observed delay for any normal sinus beat in the first 20 minutes after the onset of S-T segment changes was significantly greater in the LAD infarct group.

was progressive, so that the frequency and severity of the ventricular arrhythmia increased as did the delay in activation in the ischemic heart. Figure 7 shows the changes in epicardial delay as recorded in the experimental infarct animals with previous LAD coronary artery occlusion and reperfusion as compared with dogs with only LAD coronary artery stenosis. The peak epicardial delay in the 2 groups was observed within 10 to 12 minutes after the appearance of S-T segment changes in the lead II electrocardiograms and was significantly greater in the group with previous myocardial ischemic injury as compared with the noninfarcted control animals ($p < 0.05$). Subepicardial composite bipolar electrocardiograms of the region of distribution of the LAD coronary artery in both groups of animals were not altered initially by the subsequent development of ischemia in the myocardial region supplied by the LC coronary artery. In the 7 experimental animals with previous ischemic myocardial injury, VF developed in all after the development of ischemic S-T segment changes in the limb lead electrocardiogram and the appearance of conduction delay and fragmentation in the subepicardial composite bipolar electrograms of the region supplied by the LC coronary artery. However, in only 1 of 6 dogs with LAD coronary artery stenosis and without previous ischemic injury did VF develop in response to ischemia in the myocardial region supplied by the LC coronary artery. Maximal subepicardial delay of normally conducted beats was most pronounced in the group with previous ischemic injury in the region of the LAD coronary artery, and this group displayed a uniform potential to develop VF within 20 minutes after the onset of S-T segment changes (Fig. 7). The development and magnitude of changes in the subepicardial conduction delay appear to be related temporarily to the spontaneous occurrence of ventricular arrhythmias and VF.

Coronary artery thrombosis and irreversible myocardial ischemic injury: VF and sudden death occurred more frequently in those animals subjected to previous LAD coronary artery occlusion and reperfusion. Postmortem examination of the LC coronary artery distal to the point of electrode insertion revealed a thrombus that averaged 11 ± 7 mg. In 5 animals, no evidence of LC coronary artery thrombosis could be found at the site of intimal injury. In 12 animals the thrombus averaged less than 5 mg. Complete occlusion of the lumen of the LC artery by the thrombus was not observed in 18 of 30 animals dying suddenly. Because of instantaneous death in this group and because ischemia in the distribution of the LC existed only briefly before the onset of VF, postmortem staining of the ventricular sections with triphenyltetrazolium chloride did not reveal any evidence of irreversible ischemic injury in the LC distribution. However, because animals in the infarct group had been subjected to previous occlusion and reperfusion of the LAD coronary artery, triphenyltetrazolium staining showed an anterior wall infarct that averaged 15 ± 8% of total left ventricular mass.

In the noninfarcted control dogs subjected to LAD coronary artery stenosis, subsequent induction of intimal injury of the LC coronary artery produced a mean thrombus of 48 ± 40 mg (range 4 to 135 mg) and in 9 of 10 animals resulted in total occlusion of the vessel. The thrombus was significantly larger ($p < 0.05$) in the control group, probably because 8 of 10 animals survived 24 hours, allowing time for continued development and organization of an obstructive lesion. In only 2 of the 10 animals in this group did VF develop (Table II). Postmortem examination in the remaining 8 dogs 24 hours later showed an infarct mass in the distribution of the circumflex coronary artery which averaged 18 ± 12% of the total left ventricle. In the control group there was no evidence of myocardial tissue injury in the region of distribution of the stenosed LAD coronary artery. Furthermore, the administration of thioflavin-S just before sacrifice of the animals resulted in perfusion of the anterior wall segment supplied by the stenosed

vessel. Thus, despite total thrombotic occlusion of the LC coronary artery, in the presence of a critical stenosis in the LAD coronary vessel, VF or sudden death occurred in only 20% of the animals as compared with 97% of the animals that had chronic myocardial infarction due to previous ischemic injury resulting from occlusion and reperfusion of the LAD coronary vessel. In the latter group, fatal VF occurred despite the fact that the LC coronary artery did not always undergo total occlusion. Thus, a brief ischemic episode due to alterations in coronary artery blood flow in a region remote from a previous myocardial infarction is capable of leading to a rhythm disturbance that has the potential to initiate VF and sudden coronary death.

Discussion

Coronary artery disease is responsible for over 90% of sudden deaths occurring each year in the general population. In a study by Lie and Titus,[15] 62 to 74% of the hearts of victims of sudden and unexpected death showed evidence of acute or old myocardial infarction. Coronary artery stenosis was present in the heart in over 90% of these victims, and specialized staining methods provided evidence of acute myocardial ischemia in up to 81% of the hearts examined. McQuay et al[16] suggested that postinfarction angina might occur and contribute to death in as many as 20% of patients with fatal infarcts. The recent and elegant studies by Schuster and Bulkley[1] add further support to the concept that ischemia at a site remote from a previous myocardial infarction could contribute to sudden coronary death.

The animal model described in this report demonstrates that an acute ischemic event, when superimposed on a ventricular myocardium with a history of previous ischemic injury, can lead to an electrophysiologic disturbance culminating in VF. However, myocardial ischemia in the distribution of the LC coronary artery in the absence of a previous myocardial infarction carried a low risk of lethal arrhythmia, suggesting that disorganization of cardiac rhythm is more likely to occur in a ventricle that serves as a proper substrate for initiating and maintaining a rhythm capable of degenerating into VF. Through the use of programmed electrical stimulation, we as well as others have demonstrated that occlusion and reperfusion of the LAD coronary artery renders the canine heart susceptible in the long term to electrical induction of nonsustained or sustained ventricular tachycardia, or both.[9,10,17] Histologic examination of the myocardium subjected to occlusion and reperfusion showed viable myocardium within the necrotic region, suggesting that salvaged myocardial fibers may provide reentrant pathways causing sustained tachyarrhythmias.[17–20] Previous experimental and clinical studies have provided sufficient evidence that ventricular tachyarrhythmias in response to programmed electrical stimulation are due to reentry and less likely to be related to triggered automaticity or to other electrophysiologic mechanisms.[21–26] Data in the present study agree with previously published observations on the reentrant nature of induced arrhythmias. The existence of conduction defects in the epicardium of the infarcted canine heart after experimentally induced myocardial infarction has been described[24,27] and shown to be associated with reentrant ventricular arrhythmias which can be induced using the same techniques of programmed electrical stimulation practiced in the clinical laboratory. Thus, the animal model in which myocardial ischemic injury has resulted from occlusion and reperfusion of the LAD coronary artery renders the heart highly susceptible to sustained ventricular tachyarrhythmias which can be terminated by single or multiple electrical stimuli.

From our observations we assume that electrically induced arrhythmia arises from myocardium within or adjacent to the infarct and depends on the heterogeneous nature of the damaged tissue due to reperfusion after a period of ischemia.[17–20] This assumption is supported by our ability to regularly record the presence of continuous electrical activity originating from the ischemic zone (LC region) and bridging the diastolic interval between the initiating and reentrant beats as well as between consecutive reentrant beats. However, this disturbance alone does not explain why the chronically damaged heart is, for a variable period of time, susceptible to the development of VF. Neither we nor others[17–20] have noted any great tendency for VF to develop in the chronically damaged heart during programmed electrical stimulation in which the provocative stimuli were limited to variables that produced sustained or nonsustained ventricular tachycardia, or both. The addition of a second, albeit remote, ischemic episode due to initiation of an occlusive thrombotic event in the LC coronary artery causes an additional region of the heart to support a reentry pattern which ultimately engages the chronically injured region, thus leading to VF. It appears as if a critical mass of myocardium capable of providing a region of sufficient length to support a reentrant pathway is essential for the development and maintenance of spontaneous VF. Furthermore, regional myocardial ischemia as well as decreased collateral blood flow to the area of chronic myocardial infarction would result from a disturbance in LC coronary artery blood flow. Myocardial ischemia would decrease the threshold for the development of VF, thereby enhancing the possibility of fatal arrhythmia. In addition, tachyarrhythmia resulting from ischemia in the region of the LC coronary artery would further enhance the tendency for VF to develop.[28]

Our evidence illustrates that electrically induced injury to the LC causes regional disturbances in coronary blood flow, resulting in ectopic ventricular activity associated with continuous electrical activity as recorded with subepicardial bipolar composite electrodes in the acutely ischemic LC region. The bridging of the diastolic interval was associated with ventricular tachycardia due most likely to a reentrant mechanism as discussed herein and supported by the elegant observations of El-Sherif et al.[24,29] Subsequent to this event and just before the onset of VF, continuous diastolic electrical activity developed within the region of the LAD coronary artery. One might assume that overlapping of the 2 regions of reentry would result in

a relatively large zone of diastolic electrical activation capable of sustaining the reentrant mechanism leading to VF. This concept that a sufficient reentrant zone is required for the development of VF is supported by our observation that thrombotic occlusion of the LC coronary artery in the presence of LAD coronary artery stenosis, but without a previous myocardial infarction, seldom resulted in VF. This might be explained on the basis of a lack of a critical mass of myocardium with altered electrophysiologic properties capable of initiating and sustaining VF. Thus, the addition of a remote site of ischemia in the presence of chronic myocardial infarction may be a major factor leading to the development of VF.

We are well aware that not all authorities would agree with the interpretation of our results and the analysis of the subepicardial electrograms. We suggest that although continuous electrical activity is expected within an area of reentry, continuous activity is not, in itself, proof of reentry.[30,31] In contrast to many previous studies, we employed a composite electrode made up of an array of subepicardial recording sites. Furthermore, the electrical event being recorded is that which precedes the development of VF and is in response to an acute ischemic episode which in the majority of instances was transmural myocardial ischemia due to interruption in LC coronary artery blood flow. Using a subepicardial bipolar composite electrode recording arrangement similar to that described herein, Kaplinsky et al[32] analyzed the exact time course of ventricular arrhythmias after coronary artery ligation and correlated these events with the local disturbance of activation in the ischemic zone. Their data show that VF of immediate (first 10 minutes) ventricular arrhythmias is associated with severe subepicardial delay of the normally conducted beats, whereas VF of the delayed (12 to 30 minutes) arrhythmias was not associated with subepicardial delay. The development of VF in the model described herein is closely related to that of the immediate variety discussed by Kaplinsky et al.[32]

It is difficult to extrapolate from the animal experiment to the clinical situation. However, the animal model of "sudden coronary death" presented in this study may provide a useful tool to explore in greater detail those electrophysiologic events associated with the development of VF in a totally physiologic setting not requiring anesthesia and not being dependent on the application of external electrical stimui to initiate and sustain the development of VF. Furthermore, we view this animal model as a potentially useful adjunct in the final preclinical evaluation of pharmacologic interventions designed to prevent VF.[33]

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Quantitative Assessment of Infarct Size Reduction by Coronary Venous Retroperfusion in Baboons

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Initial favorable reports in which coronary venous retroperfusion was begun after acute coronary artery occlusion have demonstrated a reversal of ischemic injury and improved left ventricular function. However, little information has been generated to document the extent to which retroperfusion may decrease ultimate histologically determined infarct size. The objective of the present study was to evaluate the effectiveness of retroperfusion in reducing infarct size by using an accurate quantitative method in which infarct size was related to the size of the anatomic perfusion bed of the occluded artery (region at risk for infarction). In an experimental group of 5 baboons, the left anterior descending coronary artery was occluded and coronary venous retroperfusion started 1 hour after occlusion. After a 4-hour period of occlusion, retroperfusion was discontinued and anterograde perfusion was simultaneously restored. A control group of 5 baboons underwent an identical procedure without retroperfusion. Twenty-four hours after occlusion, hearts were excised and the previously occluded left anterior descending coronary artery as well as the adjacent arteries were injected with microvascular dye to delineate the perfusion bed of the occluded artery. Planimetry of serial cross-sections of the left ventricle enabled the size of the perfusion bed of the occluded artery and size of the infarct to be determined. The mean percentage of the perfusion bed infarcted in the control group was 94.1 ± 0.9 (mean ± standard error) and in the retroperfused group was 57.4 ± 3.5 ($p < 0.001$). Hence, the results demonstrated that when retroperfusion was initiated after 1 hour of coronary occlusion, the mean percentage of the perfusion bed salvaged was increased by 36.7%.

Several investigators have shown that selective synchronized coronary venous retroperfusion, when started after acute coronary artery occlusion, may result in partial reversal of ischemic injury[1–3] and improved left ventricular function.[1,2,4] Despite these favorable reports, little information has been available as to whether retroperfusion reduces infarct size as histologically assessed. In our previous study in the baboon, we demonstrated that retroperfusion begun 15 minutes after coronary artery occlusion combined with later anterograde reperfusion substantially reduced the percentage of the left ventricle ultimately infarcted.[5] Because retroperfusion was initiated early at a time when the entire ischemic region has been shown to remain viable,[6] the optimal effectiveness of the retroperfusion system was demonstrated.

The results of the initial study demonstrated the capability of the retroperfusion system to maintain the viability of ischemic myocardium. Because of these results, the next step was to examine the effectiveness when it was delayed for a period consistent with its clinical use. Therefore, the objective of the present study was to examine the effectiveness of coronary venous retroperfusion in reducing infarct size when retroperfusion was delayed for 1 hour after coronary occlusion. Additionally, a more accurate methodologic approach was employed to determine the degree of myocardial salvage achieved by retroperfusion. Infarct size was related to the size of the anatomic perfusion bed of the occluded artery (region at risk for infarction). This technique eliminated the variability in infarct size which may occur due to inherent variability in the size of the anatomic perfusion bed of an occluded artery. Thus, a

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more accurate quantitative assessment of myocardial salvage by retroperfusion may be determined.

Methods

Surgical preparation: Ten baboons (Papio anubis), 20 to 26 kg, were initially sedated with ketamine hydrochloride (10 mg/kg intramuscularly). Anesthesia was induced and maintained with intravenous infusions of sodium thiopental (2 mg/kg). A standard lead II electrocardiogram was monitored. Baboons were intubated with a cuffed endotracheal tube and ventilated with a Harvard volume respirator maintaining an arterial pH of 7.40 ± 0.05. Supplemental oxygen was administered as necessary to maintain an arterial oxygen saturation of at least 95%. Arterial pressure was monitored by an 8Fr stiff-walled catheter advanced through the left femoral artery. Intravenous fluids were administered via a catheter through the left femoral vein. A 9Fr cannula was inserted into the right femoral artery and served as the source of arterialized blood for the coronary venous retroperfusion system. A mid-sternal thoracotomy was performed and the heart suspended in a pericardial cradle. The left anterior descending coronary artery was dissected free from the anterior interventricular vein distal to the first diagonal branch. A 3-0 Mersilene® snare was placed around the dissected left anterior descending coronary artery for subsequent ligation. An electromagnetic flow catheter (Millar Instruments, Houston, Texas) was inserted into the pulmonary artery by means of a purse-string suture for measurement of cardiac output. Left ventricular pressure, the rate of rise of left ventricular pressure, and left ventricular end-diastolic pressure were monitored with use of a micromanometer tip catheter (Millar) which was inserted through a 12-gauge cannula into the left ventricle. A 6Fr thin-walled preshaped polyethylene retroperfusion catheter was inserted into the right atrium through a purse-string suture in the atrial appendage. The catheter was then advanced through the coronary sinus to position its tip at the junction of the great cardiac vein and the anterior interventricular vein. A slow infusion of heparinized saline solution was maintained through the catheter to ensure patency until retroperfusion was initiated. Two rows of 6 unipolar atraumatic epicardial electrodes spaced at 5 mm intervals were placed across the anticipated region of ischemia parallel to the minor axis of the left ventricle. Recordings from the electrode rows were used to assess directional changes in S-T segment elevation during periods of occlusion, retroperfusion, and anterograde reperfusion.

Coronary venous retroperfusion system: The coronary venous retroperfusion system is schematically illustrated in Figure 1. It is similar to our previously described system[5] except that a commercially available pulsatile pump and pumping chamber were employed. The right femoral artery served as the source of arterial blood which flowed through an occlusive roller pump calibrated to accurately deliver the small required blood flow rates. The roller pump provided a continuous blood flow of 40 to 50 ml/min into a bladder contained within a pediatric pulsatile bypass chamber (Kontron Cardiovascular, Everett, Massachusetts). The chamber contains 2 bladders; 1 is connected to the roller pump and the other is connected to a pulsatile bypass pump (Model 20, Kontron Cardiovascular) which provides active compression and decompression of the blood-filled bladder. Arterialized blood from the bladder was pumped in a pulsatile manner through the retroperfusion catheter positioned in the great cardiac vein. A Statham P23 Db pressure transducer was connected between the pumping chamber and the retroperfusion catheter to assist in monitoring venous perfusion pressures. These pressures directly reflect the pressures in the coronary veins. An elevation in pressure may occur due either to wedging of the catheter in the coronary veins or inadequate drainage due to the flow rate being set too high. If the flow was set at >50 ml/min, the retroperfusion pump was usually not able to deliver the required volume during the diastolic compression phase. Consequently flow would continue into the coronary veins during systole, resulting in inadequate drainage and an elevation in pressure. We previously showed

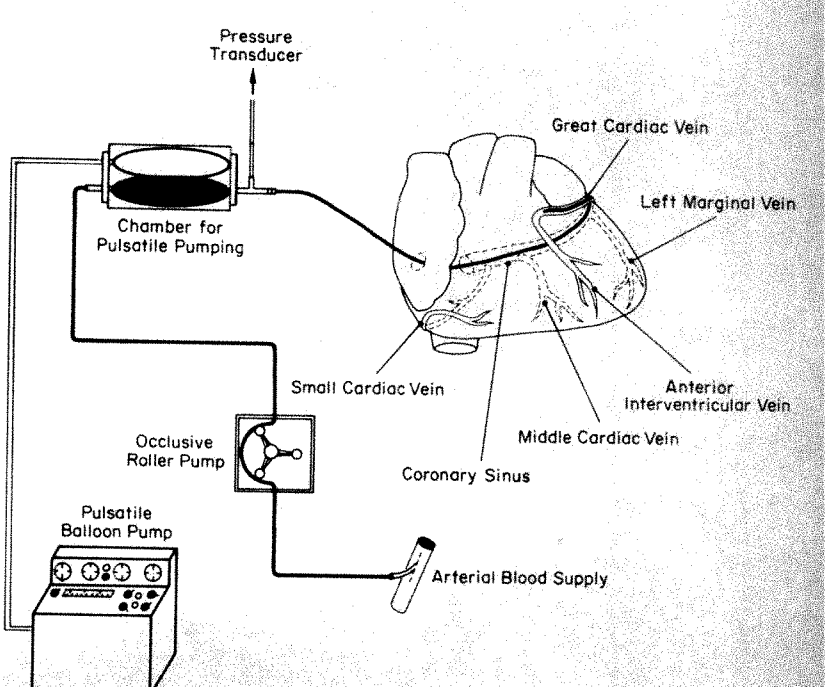

FIGURE 1. Diagram of the retroperfusion system. See text for detailed description.

that a flow rate of 40 to 50 ml/min produced adequate rearterialization.[5] We did not simultaneously record the pressures in the coronary veins as this would have required insertion of a separate line for pressure recording. However, in preliminary experiments, we monitored pressure in the anterior interventricular vein during retroperfusion with flows up to 60 ml/min and found the pressure <50 mm Hg.

The pulsatile pump system was adjusted so that forward pulsed perfusion occurred only in diastole and perfusion was interrupted during systole so that normal coronary venous drainage was allowed. This was accomplished by simultaneously displaying the left ventricular pressure and the retroperfusion pressure tracings so the retroperfusion pulse could be adjusted to occur during the diastolic interval. Anticoagulation was maintained during the period of retroperfusion by initial heparinization (5 mg/kg intravenously), with supplemental intravenous heparin administered to maintain the activated clotting time at 350 to 500 seconds to prevent blood clotting in the retroperfusion system.

Study protocol: An experimental group of 5 baboons underwent coronary venous retroperfusion. Control baseline hemodynamic recordings and epicardial electrograms were monitored for 30 minutes before coronary occlusion. The left anterior descending coronary artery was then occluded, and hemodynamic and electrocardiographic recordings were obtained every 15 minutes throughout the experiment. Coronary venous retroperfusion was initiated after 1 hour of occlusion and maintained through a 4-hour period of coronary artery occlusion. When retroperfusion was ended, anterograde perfusion was simultaneously restored by release of the occluding snare. The retroperfusion catheter was then removed, and protamine sulfate was administered to return the activated clotting time to the control level. After a 1-hour reperfusion monitoring period, the epicardial electrodes as well as the cardiac output and left ventricular pressure catheters were removed. The chest was closed while monitoring arterial pressure and the electrocardiogram. The remaining indwelling lines were then removed and the baboons returned to their cages. At 24 hours after occlusion the baboons were killed by rapid infusion of a saturated solution of potassium chloride and their hearts were excised for histologic analysis.

A control group of 5 baboons underwent an identical protocol to that utilized in the experimental group including placement of the coronary venous retroperfusion catheter and heparinization. In this group, however, no retroperfusion was initiated. Anterograde reperfusion was restored after 4 hours of coronary occlusion.

Perfusion bed delineation and histologic assessment: Cannulas (0.58 mm internal diameter) were placed into (1) the left anterior descending coronary artery at the site of previous occlusion, (2) the proximal left anterior descending artery, (3) the proximal left circumflex artery, and (4) the proximal right coronary artery. These arteries were then injected simultaneously and at equal flow rates with colored silicone rubber microvascular dyes (Microfil, Canton Bio-Medical Products, Boulder, Colorado) which readily pass through the capillary beds.[7] We previously showed that this dye injection technique allows accurate delineation of the perfusion bed subserved by an occluded coronary artery.[8] After fixation of the hearts in 10% formalin for 3 days, serial cross-sections of the left ventricle were made at 3 mm intervals parallel to the minor axis. A microscopic slide was made from each cross-section and stained with hematoxylin and eosin. The perfusion bed of the occluded artery was clearly visualized on the paraffin tissue block of the left ventricular cross-section and was marked on the corresponding histologic slide by superimposing the slide on the tissue block. Microscopic examination of each histologic slide allowed the area of infarction to be also marked on the slide. The areas of the perfusion bed and the areas of infarction were determined by planimetry. These areas were multiplied by the thickness of each cross-section to give the respective volumes for each section. Summation of the volumes of each tissue section yielded the total volume of the perfusion bed and the total volume of infarction for each heart. These values were multiplied by the tissue density to yield the mass of the perfusion bed and the mass of infarct.

Statistical analysis: The significance of hemodynamic and histologic changes between control and retroperfused baboons was examined using Student's t test. All values are given as mean ± standard error of the mean.

Results

After occlusion of the left anterior descending coronary artery in all 10 baboons, a discrete area of the anterior left ventricular wall appeared visibly cyanotic. In the retroperfused baboons, with the initiation of coronary venous retroperfusion, the anterior interventricular vein was visibly arterialized, and resolution of the area of ventricular cyanosis occurred. With release of the occluding snare 4 hours after occlusion, rearterialization occurred promptly in the previously occluded coronary artery in all baboons.

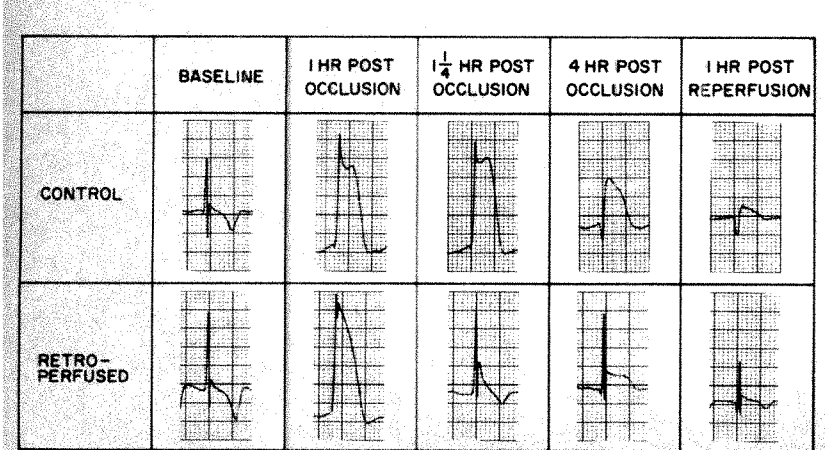

FIGURE 2. The progression of electrocardiographic changes during the periods of occlusion and reperfusion are shown for a representative control baboon and a retroperfused baboon. No significant S-T segment elevation was present before occlusion in either baboon. One hour after occlusion there were markedly elevated S-T segments in both the control and retroperfused baboons. At 1 1/4 hours after occlusion (15 minutes after the initiation of retroperfusion), there was a significant reduction in S-T segment elevation in the retroperfused baboon with no significant change in S-T segment elevation in the control nonretroperfused baboon. Four hours after occlusion, immediately before reperfusion, the S-T segment in the control baboon remained elevated while the S-T segment in the retroperfused baboon was near baseline. One hour after reperfusion, the control baboon had lost most of its R-wave amplitude and developed a Q wave while the retroperfused baboon retained significant R-wave amplitude and did not develop a Q wave.

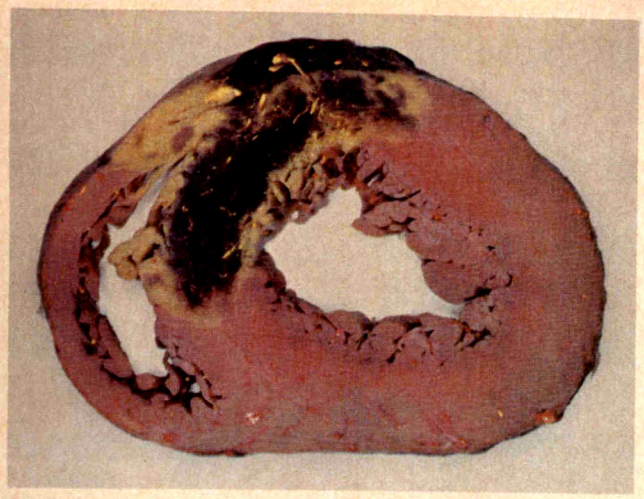

FIGURE 3. Representative cross-section of the heart from a control baboon with a 4-hour occlusion of the left anterior descending coronary artery followed by reperfusion. The perfusion bed of the previously occluded artery was injected with yellow microvascular dye and the adjacent perfusion beds with red dye. The perfusion bed of the occluded artery is readily delineated and contains a large hemorrhagic region which occupies virtually the entire perfusion bed.

Epicardial electrocardiographic recordings: The progression of electrocardiographic changes during the periods of occlusion and reperfusion for a representative control and retroperfused baboon are shown in Figure 2. There was no significant S-T segment elevation in any of the epicardial leads in either group immediately before occlusion. S-T segment elevation occurred in epicardial leads in the area of ventricular cyanosis within minutes after occlusion of the left anterior descending coronary artery. In the retroperfused baboons, S-T segment elevation decreased rapidly to near control values after the initiation of coronary venous retroperfusion. In the control group, S-T segments remained elevated throughout the 4-hour period of occlusion. In both groups, the remaining S-T segment elevation steadily decreased during the 1-hour period of anterograde reperfusion, although S-T segments sometimes remained slightly elevated in the control baboons.

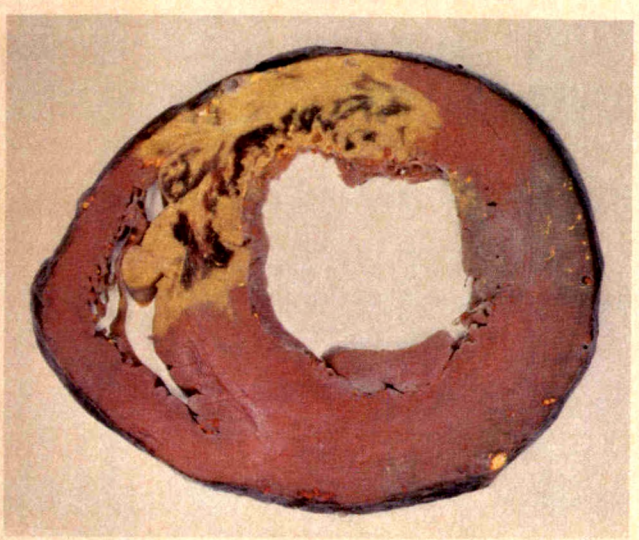

FIGURE 4. Representative cross-section of the heart from a retroperfused baboon. Retroperfusion was iniitated 1 hour after occlusion of the left anterior descending coronary artery and maintained for a 4-hour period of occlusion followed by reperfusion. The perfusion bed of the occluded artery is readily delineated by the yellow dye and contains patchy areas of hemorrhage in the subendocardial and mid-wall regions.

Delineation of the perfusion bed of the occluded coronary artery: Cross-sections of the left ventricle in both control and retroperfused baboons showed the perfusion bed of the occluded coronary artery to be readily delineated by the microvascular dye. A representative cross-section of the heart from a control baboon, shown in Figure 3, demonstrates the distinct demarcation of perfusion bed boundaries as well as the extensive hemorrhage which occupied virtually the entire perfusion bed of the occluded artery. Figure 4 shows a representative cross-section of the heart from a retroperfused baboon and again illustrates the distinct demarcation of the perfusion bed boundaries. In contrast to the control group of baboons, however, hemorrhage was confined to the subendocardial and mid-wall regions of the perfusion bed.

Comparison of histologic changes in control and retroperfused baboons: Microscopic examination of hematoxylin and eosin-stained left ventricular cross-sections in control baboons showed extensive coagulation necrosis which essentially occupied the entire perfusion bed of the occluded artery. The area of infarction was completely contained within the perfusion bed. Necrotic myocardial cells exhibited the characteristic changes of pyknosis, karyolysis, and loss of cross-striations. There was extensive hemorrhage within the infarcted region.

Microscopic examination of left ventricular cross-sections in the retroperfused baboons showed that the area of infarction was also completely contained within the perfusion bed of the occluded artery. Infarcts characteristically consisted of a central confluent zone of infarction surrounded by a peripheral zone of small foci of patchy infarction. The infarcts showed coagulation necrosis and involved the subendocardial and mid-wall regions of the perfusion bed, while myocardial preservation was observed in the subepicardial and lateral regions. Hemorrhage was evident within the central area of infarction; however, no hemorrhage was observed outside the infarcted region. In the retroperfused baboons, minimal venous hemorrhage was often evident close to veins at the epicardial surface and particularly those close to the retroperfusion catheter. This hemorrhage did not extend below the epicardial surface. There was no gross evidence of damage to the coronary veins in either group of baboons.

Comparison of the percentage of the perfusion bed infarcted in control and retroperfused baboons: Table I shows the mass of the perfusion bed, the mass of the infarct, and the mass of hemorrhage for individual

TABLE I Comparison of Data on the Control and Retroperfused Baboons

Baboon	Perfusion Bed Mass (g)	Infarct Mass (g)	% of Perfusion Bed Infarcted	Hemorrhagic Mass (g)	% of Perfusion Bed Hemorrhagic
			Control		
1	25.3	23.7	93.6	18.2	71.9
2	15.1	13.8	91.9	8.7	57.6
3	14.3	13.7	95.5	8.5	59.2
4	19.3	18.7	96.5	14.6	75.4
5	15.4	14.3	92.8	8.4	54.2
	17.9 ± 2.0	16.8 ± 2.0	94.1 ± 0.9	11.7 ± 2.0	63.7 ± 4.2
			Retroperfused		
1	40.7	20.3	49.9	8.6	21.0
2	4.7	2.8	58.1	0.1	1.0
3	11.7	6.4	52.8	0.0	0.0
4	16.8	11.1	70.1	2.6	15.7
5	9.9	5.5	55.9	1.1	11.3
	16.8 ± 6.3	9.2 ± 3.1	57.4 ± 3.5*	2.5 ± 1.6*	9.8 ± 4.1*

* Significant difference ($p < 0.001$) between control and retroperfused groups.

baboons in both groups. A substantial reduction was observed in the percentage of the anatomic perfusion bed infarcted in the retroperfused baboons when compared to that in the control nonretroperfused baboons. The mean perfusion bed mass was 17.9 ± 2.0 g in the control baboons and 16.8 ± 6.3 g in the retroperfused baboons. These values are not statistically different ($p > 0.1$). In the control group, the mean percentage of the perfusion bed infarcted was 94.1 ± 0.9. In the retroperfused group, the mean percentage of the perfusion bed infarcted was 57.4 ± 3.5. This difference was highly significant ($p < 0.001$). Hence, with retroperfusion begun after 1 hour of coronary occlusion, the area of the perfusion bed undergoing ultimate infarction was reduced by a mean of 36.7% when comparing the control and retroperfused groups.

Hemorrhage was always contained within the infarct region and the mean percentage of the perfusion bed that was hemorrhagic was significantly lower than the mean percentage of the perfusion bed infarcted in both control and retroperfused groups ($p < 0.001$). In the control group, the mean percentage of the perfusion bed that was hemorrhagic was 63.7 ± 4.2; in the retroperfused group the mean percentage of the perfusion bed that was hemorrhagic was 9.8 ± 4.1. This difference was also highly significant ($p < 0.001$).

Hemodynamic changes: Table II summarizes the hemodynamic values in the control and retroperfused baboons for the preocclusion, 15-minute postocclusion, 4-hour postocclusion (before ending retroperfusion), and 1-hour postreperfusion recording periods. At the preocclusion recording period, there was no significant differences in any of the hemodynamic values in control and retroperfusion baboons. There were no significant changes from the preocclusion recording period in any of the hemodynamic values in the control or retroperfused groups at any of the recording periods.

Discussion

The coronary veins have been utilized as a means of rearterialization of a region of myocardial ischemia since the initial experimental and clinical observations of Beck et al[9,10] and others.[11,12] The concept of selective rather than global coronary venous retroperfusion, to-

TABLE II Hemodynamic Values Before and After Occlusion and After Reperfusion for the Control and Retroperfusion Baboons

		Before Occlusion	After Occlusion		1 Hour After Reperfusion
			15 Minutes	4 Hours	
HR (beats/min)	Control	124 ± 4	128 ± 6	125 ± 4	124 ± 5
	Retroperfused	110 ± 3	112 ± 4	107 ± 6	106 ± 7
$\overline{AP}$ (mm Hg)	Control	117 ± 4	123 ± 7	114 ± 3	112 ± 6
	Retroperfused	108 ± 4	107 ± 3	100 ± 6	106 ± 6
LVEDP (mm Hg)	Control	5.3 ± 1.0	8.0 ± 3.3	4.6 ± 1.0	5.4 ± 0.8
	Retroperfused	4.4 ± 0.9	4.0 ± 1.4	4.8 ± 1.9	5.0 ± 1.0
CO (ml/min)	Control	1,831 ± 215	1,950 ± 180	1,860 ± 262	1,770 ± 378
	Retroperfused	1,700 ± 265	1,710 ± 105	1,450 ± 180	1,550 ± 132
Peak dP/dt (mm Hg/s	Control	2,180 ± 156	1,848 ± 221	1,880 ± 153	1,840 ± 172
	Retroperfused	1,888 ± 254	1,436 ± 192	1,748 ± 297	1,896 ± 262

$\overline{AP}$ = mean arterial pressure; CO = cardiac output; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; peak dP/dt = peak value of rate of rise of left ventricular pressure.

gether with the identification of a group of patients with severe chronic arterial disease not amenable to coronary bypass grafting, led to surgical procedures aimed at selective arterialization of the coronary venous system.[13–17] Subsequently, several investigators modified this concept and employed retroperfusion by selective catheterization of the coronary venous system to reverse ischemia following acute coronary artery occlusion.[1–4,18] These systems have employed pulsatile venous retroperfusion which is synchronized with the cardiac cycle, so that the retrograde arterial pulse is programmed to occur during diastole and is discontinued during systole to allow for adequate venous drainage. These studies have demonstrated that after the initiation of retroperfusion, there is (1) a reduction in epicardial S-T segment elevation,[1,3,4,18] (2) improved myocardial oxygen tension in the ischemic segment,[3,4] (3) improved function in the ischemic segment,[2,4] and (4) an increase in global left ventricular function.[1,2] However, despite these favorable reports, little information has been generated to document the extent to which retroperfusion may decrease ultimate histologically determined infarct size. Therefore, the present study evaluated the effectiveness of retroperfusion in reducing infarct size when begun 1 hour after occlusion and maintained throughout a total 4-hour period of coronary occlusion. Additionally, infarct size was related to the size of the anatomic perfusion bed of the occluded artery (region at risk to infarction) for a more accurate assessment of the effects of retroperfusion on infarct size.

Quantitative method of determining myocardial salvage due to coronary venous retroperfusion: It has been shown considerable variability exists in infarct size resulting from coronary artery occlusion at any given anatomic site.[19,20] This variability results from differences in the region at risk to infarction due to inherent differences in the size of the anatomic perfusion bed subserved by an occluded artery. We have previously demonstrated in the baboon that the microvascular dye technique employed in this study accurately delineates the anatomic perfusion bed of the occluded artery.[8] By comparing the percentage of the perfusion bed of the occluded artery which undergoes infarction in control and retroperfused baboons, an accurate quantitative assessment of the degree of myocardial salvage achieved by retroperfusion may be determined.

Effectiveness of coronary venous retroperfusion in reducing infarct size: We previously demonstrated in the baboon that retroperfusion started at 15 minutes after coronary occlusion and maintained for a total 4-hour period of occlusion resulted in an 84% mean reduction in infarct size.[5] Because retroperfusion was initiated early, before the onset of necrosis within the ischemic region, the optimal effectiveness of retroperfusion was demonstrated in the study. In the present study, retroperfusion was begun 1 hour after occlusion and resulted in a 36.7% mean reduction in infarct size. Thus, the delay from the onset of coronary occlusion to the initiation of retroperfusion is a critical determinant of the degree of myocardial salvage.

Comparison of anterograde arterial reperfusion versus coronary venous retroperfusion in reducing infarct size: The degree of myocardial salvage with anterograde arterial *reperfusion* depends on the time reperfusion is begun. The degree of myocardial salvage with *retroperfusion* depends not only on the time retroperfusion is begun, but also on how effectively the retroperfusion system is capable of delivering arterial blood to the ischemic region. Thus, it is interesting to examine how closely coronary venous retroperfusion approaches the effectiveness of arterial reperfusion in reducing infarct size.

In order for coronary venous retroperfusion to be effective, it must deliver sufficient arterial blood to all levels of the myocardial wall within the ischemic region to satisfy the oxygen demands of this region. A number of studies using injection of various contrast agents have indirectly suggested that retroperfused blood is effectively delivered to the ischemic region.[21,22] The studies of Hochberg et al[16,23] using radioactive microspheres demonstrated that retrograde arterial blood flow is distributed to all levels of an acutely ischemic region and not significantly shunted by thebesian or veno-venous channels. More recently, Berdeaux et al,[18] also using microspheres, demonstrated that retroperfusion initiated at 1 hour after coronary occlusion returned transmural flow in the ischemic region to 45% of the normal control flow which existed before coronary occlusion. The results of this study of Berdeaux et al[18] bear directly on the question of whether this degree of restoration of flow is sufficient to substantially prolong myocardial viability.

This question may be clarified by directly comparing the degree of infarct salvage achieved by anterograde reperfusion with the degree of infarct salvage achieved by retroperfusion instituted at comparable times after acute coronary occlusion. We have shown in the baboon that with anterograde reperfusion 2 hours after coronary occlusion, a mean of 50.1% of the perfusion bed of the occluded artery was infarcted.[24] With retroperfusion 1 hour after coronary occlusion in the present study, a mean of 57.4% of the perfusion bed of the occluded artery was infarcted. It is interesting that with retroperfusion 1 hour after coronary occlusion, the percentage of the perfusion bed infarcted was approximately the same as that found with anterograde reperfusion 2 hours after occlusion. This finding is consistent with the observation by Berdeaux et al[18] that retroperfusion initiated 1 hour after coronary occlusion was capable of restoring blood flow to only 45% of the normal control flow.

Hemorrhage associated with retroperfusion: Is hemorrhage associated with retroperfusion deleterious to ischemic myocardium? Although the infarcts in the retroperfused baboons were hemorrhagic, the hemorrhage was confined within the infarcted region and did not appear to extend the infarct. This observation is similar to that noted with anterograde reperfusion; several investigators have demonstrated that hemorrhage after reperfusion does not extend infarct size.[25–28] Some hemorrhage was noted around superficial veins,

but it did not extend below the epicardial surface and there was no gross damage to the coronary veins.

Clinical application of coronary venous retroperfusion: Experimental animal studies suggest that anterograde reperfusion must be undertaken within the first few hours after coronary occlusion for significant salvage of ischemic myocardium to occur.[24,25,29] The time interval in the clinical setting in which restoration of perfusion salvages significant myocardium remains unclear but may be longer than experimental animal studies suggest. Hence, retroperfusion may be useful clinically as a simple and prompt method to temporarily rearterialize an acutely ischemic region until such time as more definitive revascularization may be undertaken. It is also noted that coronary venous retroperfusion may be useful by providing a potential avenue for the introduction of pharmacologic agents directly into the ischemic region.

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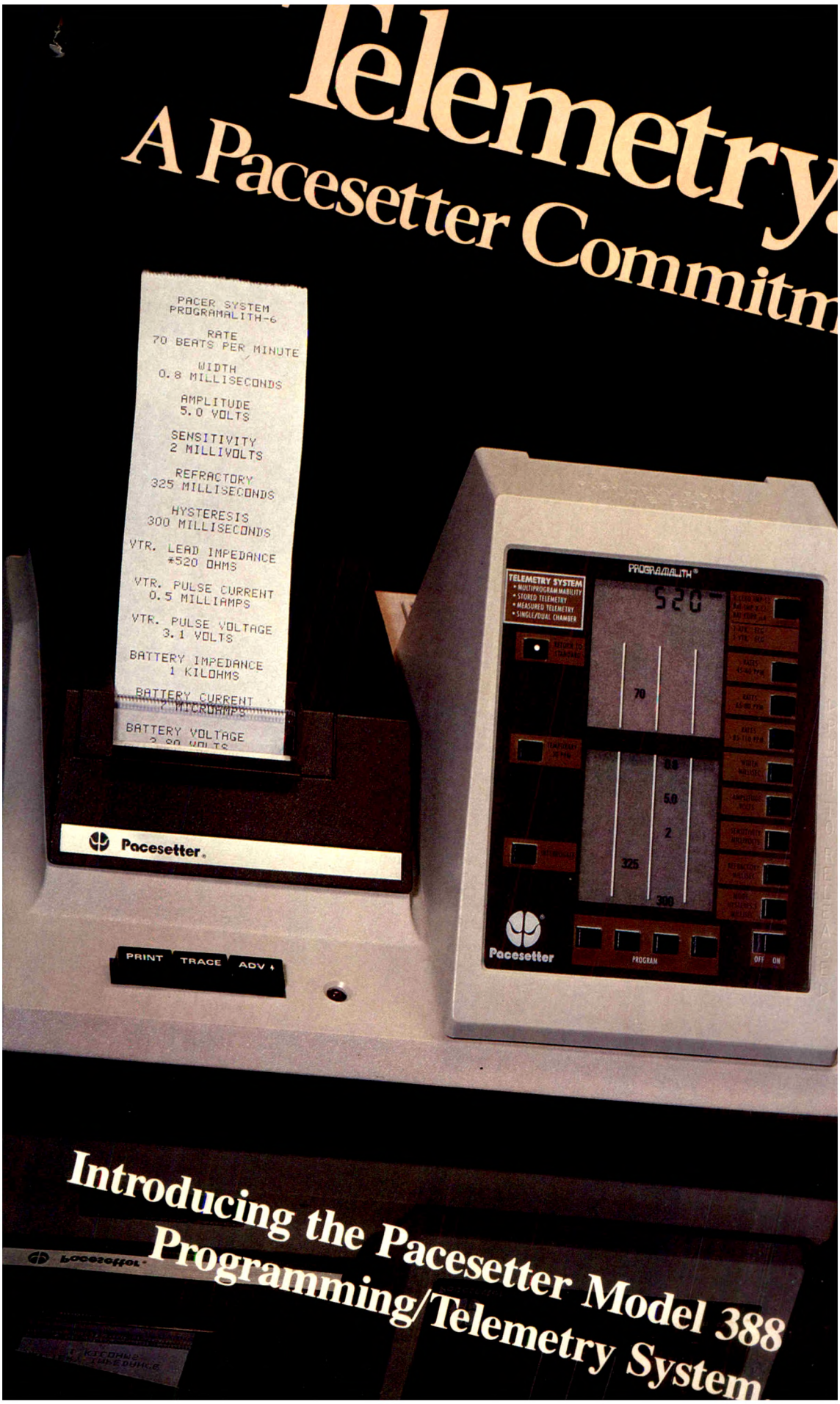
Telemetry.
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WIDTH
0.8 MILLISECONDS
AMPLITUDE
5.0 VOLTS
SENSITIVITY
2 MILLIVOLTS
REFRACTORY
325 MILLISECONDS
HYSTERESIS
300 MILLISECONDS
VTR. LEAD IMPEDANCE
*520 OHMS
VTR. PULSE CURRENT
0.5 MILLIAMPS
VTR. PULSE VOLTAGE
3.1 VOLTS
BATTERY IMPEDANCE
1 KILOHMS
BATTERY CURRENT
MICROAMPS
BATTERY VOLTAGE
Pacesetter.
PRINT
TRACE
ADV
PROGRAMALITH
TELEMETRY SYSTEM
• MULTIPROGRAMMABILITY
• STORED TELEMETRY
• MEASURED TELEMETRY
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70
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5.0
2
325
300
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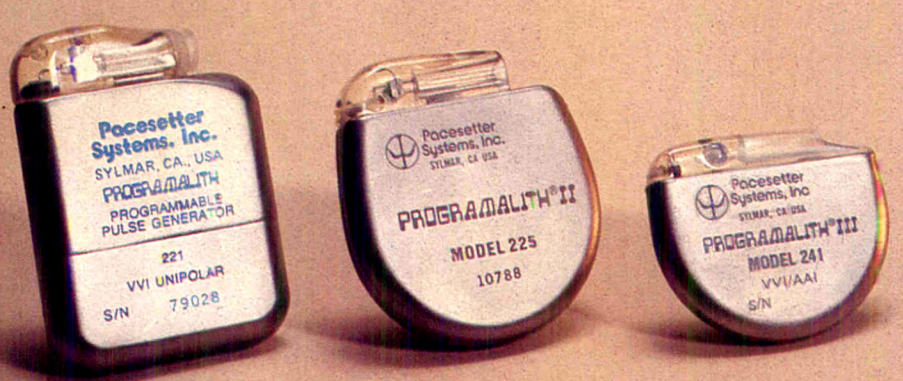
Compatability. The Model 388 Extended Programming/Telemetry System allows multi-parameter programming with three types of telemetry information for all Programalith pulse generators, in both single- and dual-chamber configurations: Programalith I, Programalith II, and Programalith III.



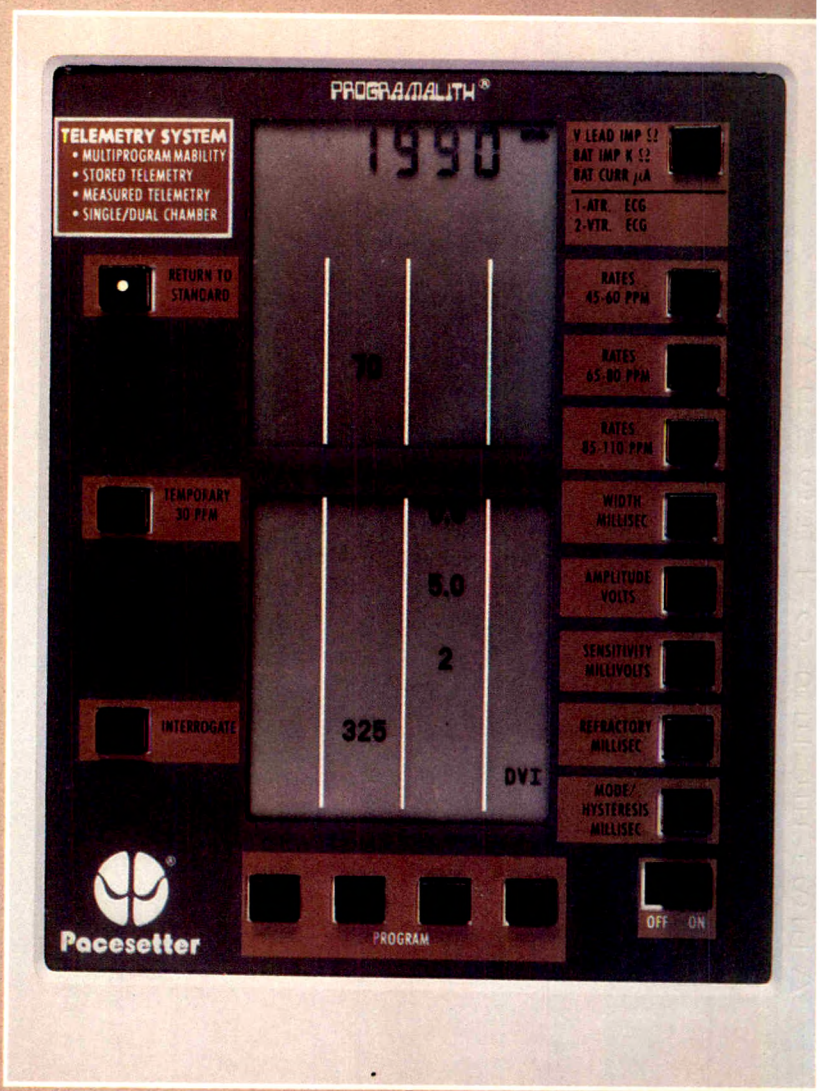
Pictured left: Programalith I, Programalith II and Programalith III.

Pacesetter expands it telemetry system– and our commitment

The Commitment.

The Pacesetter Programalith® system, the world's first with functional bi-directional telemetry, has been the leading example of advanced pacemaker technology since its introduction. Now, with the introduction of the Pacesetter Model 388 Extended Programming/ Telemetry System, that technology –and that leadership—have been expanded.

Perhaps most important of all is the unique design concept behind the Model 388, which provides more telemetered data retrieval from newer Pacesetter pulse generators, and retrieves additional telemetry information from previously implanted Programalith models. This concept—that our research and development efforts be applied to existing products as well as to new products—is at the heart of Pacesetter's commitment.



The Programalith A-V pulse generator, shown actual size. Readout on faceplate of Model 388 Programming/ Telemetry System, illustrating display of telemetry data, with no lead in pulse generator.

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nother reason we're called PACE*SETTER*:

The Pacesetter Model 388 Programming/Telemetry System

Functional Description

MODEL IMPLANTED	PROGRAMMABLE PARAMETERS	PROGRAMMED (STORED) TELEMETRY VALUES 398 and 388 Provide	MEASURED TELEMETRY VALUES 398 Provides	MEASURED TELEMETRY VALUES 388 Retrieves Additionally	INTRACARDIAC ELECTROGRAM 398 Provides	INTRACARDIAC ELECTROGRAM 388 Provides
PROGRAMALITH® I or II						
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Tribute to Paul Wood

E. GREY DIMOND, MD

We were at morning report and the residents and senior medical students were gathered. A young patient with atrial fibrillation had been admitted during the night. The episode had begun suddenly and had never occurred before. The resident expressed surprise at the amount of urine the patient had passed since admission and said, "We will work him up for heart failure and diabetes." Without guile, I said, "But isn't this a classic example of the polyuria with lone fibrillation that Wood described?" There was silence, and then from the back of the room a hesitant voice asked, "Who's Wood?"

I laughed, not quite sensing the dimension of the query, and asked if someone would look up the reference and tell us about it the next morning. Morning report ended, and the senior resident sought me out, with pen in hand. He said, "Where do I find this Wood reference? What journal is it in? Where is he?" The senior resident was sincere and I told him to go to the *British Heart Journal* of the early 1960s. He whistled in surprise that this was indeed a historical source.

The next morning, we began morning report by my comment and query: "Yesterday we talked over the case of a young man with an episode of atrial fibrillation and diuresis. Our senior resident will give us a report on his review of the literature. Before he does, I want to ask 3 questions so we can all know our shared information base." I asked for a show of hands of those present who used the term "lone" atrial fibrillation (no hands), those who had heard of Dr. Willie Evans (no hands), those who had heard of Paul Wood (one hand—that of the resident I had sent to the library). There were 16 residents present, from 11 medical schools.

This experience was in the spring of 1982, and I mulled, thought, reflected, and sighed for several days. I pulled out the 2 articles, just to be sure that my memory was valid: "Lone Auricular Fibrillation," by W. Evans and P. Swann, *British Heart Journal* 1959;16:189; and "Polyuria in Paroxysmal Tachycardia and Paroxysmal Atrial Fibrillation," by Paul Wood, *British Heart Journal*, 1963;25:273.

So, these articles did exist; it was not all a mirage of things past. However, my attention was caught by the footnote on Wood's article of 1963. Maurice Campbell, then the Editor of the *British Heart Journal*, had added a note that he had edited this article for Paul Wood, and it was published posthumously.

I paused, as if I had felt a gentle shock. I suddenly remembered that 1962 was indeed the year of Wood's death—and my conversation with the residents was occurring within a few months of the 20th anniversary of his death. The oldest of the residents would have been 6 or 7 years old when Wood died.

For the next several days a lingering sadness weighed on me. I pulled down from my shelf his book and also the memorial that his friends had written on the 10th anniversary of his death. I read these, and it was vivid again what a dynamic force he had been in the world of cardiology. Others did the great surgical feats or brought forth new technical procedures, but one man alone was the talent who absorbed the potential of the new tools of catheter, angiography and phonocardiography, tamed them, and showed how a clinician could frame their messages into clinical algorithms.

Wood came back from the War and by January 1950 had accomplished the intellectual feat of bringing technique and clinical skills together to define a new kind of dynamic cardiology. His book was at once a physiologic statement of his clinical mastery, and a flag to all the world that there was a new leader in diagnostic cardiology, and he was in London and his name was Paul Wood.

To grasp the sheer energy involved, one must remember he was born in India, raised in Tasmania, schooled in Australia, house officered in New Zealand, and gave 5 years to military service; but this book and the enormous clinical and laboratory experience behind it was accomplished by age 43. If one credits Paul White's classic text with establishing the dimensions, the vocabulary, and almost the definitions of cardiology; and Friedberg's book with expressing a single physician's clinical experience within these parameters; then Wood's book was the landmark in print announcing the new era of physiologic, morphologic, dynamic cardiology. It was a point in time, gathering together the vast data accumulated from laboratories and autopsies, giving it a bedside logic, and making it possible for the bedside clinician to define the altered anatomy and physiology which the cardiac surgeon would face. In a certain sense it, this book created the era of aggressive intervention in cardiology.

Wood's colleague, Evan Bedford, expressed this sentiment exactly in words written after Wood's death: "The publication of his textbook . . . in 1950 was a great achievement after absence on war service abroad, and had the same profound influence on cardiology as Paul White's book had 20 years earlier. It reflected Wood's personal teaching, based on the meticulous analysis of his own cases. . . . From the moment I first perused the book, I realized that it was a masterly exposition . . . and it quickly became a best-seller."

Paul Wood's "Preface," dated January 1950, is but 1 page long, and if my Editor would permit, I would offer it as the single illustration of this article. However, the last paragraph

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must be quoted, for it was *the* Paul Wood message—a message that 20 years has made even more imperative to repeat: "In presenting this book I have attempted to maintain a proper balance between man and his instruments, between experienced opinion and statistics, between traditional views and the heterodox, between bedside medicine and special tests, between the practical and the academic; and so link the past with the present."

His book of 1950, and its second revised edition of 1952, did just what he stated as his purpose. Now there are 3 large textbooks of English language cardiology, all American, and all assembled from a large cuvée of cardiologists. For 20 years no one has again attempted to do what Wood did, and perhaps no one should. In 1950 he brought together the essence of bedside cardiology and defined a relationship between altered morphology and the laboratory methods which had poured a flood of data and formulas. In the 20 years since his death, the torrent of new technology has fragmented cardiology, so perhaps no one again will in a single person encompass both exquisite clinical skill and mastership of all the hardware.

The year he died, he came to the United States as the honored overseas guest of the American College of Cardiology. I was its president that year, and he and I had 7 special days together. The date was mid-June 1962, and we talked of our futures. He was gravely concerned about what he should, or could, do with the remaining years of his career. He said he knew he had made a real contribution in making the work from the laboratory clinically useful. He could not see himself taking on the new era of biochemistry, muscle physiology, and electronic instrumentation. He believed that was for the next generation of physicians. He was, he said, like a boxer who has won but now knows it's time to stop, but the momentum of his followers forces him on. We talked, shared, planned, agreed—and the next month he was dead.

He died at age 54, just 12 years after the publication of his book. If he had lived, he would now be but 74—the right age for tapering a career, and therefore one could say he died too young and he was denied the pleasure and honors these 20 years would have brought him. Maudlin it may be, but I don't believe he would have felt that way. The author of Wood's obituary in the *British Medical Journal*, written in 1962, caught this same feeling: "One suspects now, knowing all the facts, that P.W. would not have been critical of his own lot, and he would have discounted any tragedy in it." That was written by Walter Somerville, who knew Wood well and also was his physician from the hour of his attack until his death, within the week.

A great tradition of Medicine is the honoring of our predecessors. Such a tradition kept itself alive naturally and easily in the past, when it was impossible to dispute the "experienced opinion" of the older clinician, simply because he had lived longer and seen more—and when precision diagnosis by instrument was not epidemic and technical intervention the norm. It was easier for the elder to maintain his role as a resource for the oncoming young man, when the respected tools of the clinician were experience, time, and seniority. He could command the scene, measuring securely his opinion against that of the younger man.

Today, experience and maturity have eroded rights; the younger man, with his biochemical knowledge, his electronics knowledge, his computers, his pumps, his host of precision instruments, his spider skein of monitoring tubes, can, instead of honoring the old clinician, with deadliness devastate him, making him insecure and timid and, in fact, seize the scene from the patriarch.

We live in an era where experience, judgment, and wisdom do not gain for the older clinician a position of trust, but instead all are too often considered a cover-up for technical obsolescence. And there indeed is the tragedy of modern medicine. The timorous query from the back of the room, "Who's Wood?," said it all. There is no turning back the clock, and an older man risks the corridor asides of house staff suggesting that his seasoned sentiment is but the drawing shade of time. . . . But one wishes that every chief of every medical service had a required showing of the *Jugular Venous Pulse* by Paul Wood. The wisest of the house officers would gain a hint of what is being lost and what were the special abilities of Paul Wood.

The Early Pathophysiologic Understanding of Angina Pectoris

PAUL KLIGFIELD, MD

Caleb Hillier Parry of Bath and Allan Burns of Glasgow formulated explanations of angina pectoris that stand as brilliant early examples of pathophysiologic reasoning. These astute observers proposed the concept that symptomatic ischemic heart disease results from a dynamic imbalance of myocardial energy supply and demand. Their work forms the basis of our traditional understanding of effort-related chest pain in obstructive coronary artery disease.

William Heberden's masterful clinical description of 20 cases of angina pectoris,[1] published in the *Medical Transactions* in 1772, is well known to most physicians. However, it is not well appreciated that within 30 years of his original observations, a pathophysiologic understanding of angina as an imbalance in myocardial energy supply and demand had become clearly formulated by other British clinicians. Although the morbid anatomic association of angina pectoris with obstructive disease of the coronary arteries was first understood clearly by Edward Jenner, dynamic insight into the pathophysiology of myocardial ischemia was first supplied by Jenner's childhood schoolmate, Caleb Hillier Parry, at the end of the 18th century. Ten years after Parry, Allan Burns explained the concept of effort-induced angina as a symptomatic imbalance of cardiac energy supply and demand, by means of experimental analogy to ischemic limb pain occurring during claudication.

Edward Jenner

Although it is clear that John Hunter, perhaps the most eminent English anatomist of the late 18th century, performed the earliest autopsies on patients dying with a history of angina pectoris, it is doubtful that he clearly perceived the relation of coronary obstruction to the disease. Hunter's pupil Edward Jenner, however, became convinced of this association but withheld his opinion from print because he feared it would deprive Hunter, who had progressive angina, of hope of recovery.[2] Jenner, of course, remains best known for his immortal *Inquiry Into the Causes and Effects of the Variolae Vaccinae*,[3] which introduced the practice of vaccination against smallpox and was dedicated to his friend, Caleb Hillier Parry.

Jenner's striking description of remarkable autopsy findings in an early case of angina pectoris was communicated to Parry by letter in about 1785. "My knife struck something so hard and gritty as to notch it," he wrote. "I well remember looking up at the ceiling, which was old and crumbling, conceiving that some plaster had fallen down. But on further scrutiny the real cause appeared; the coronaries were become bony canals." Yet Jenner, whose subsequent experience confirmed the presence of diseased coronary arteries in other cases of angina, did not propose a mechanism to account for this association.

Caleb Hillier Parry

Caleb Hillier Parry and Edward Jenner had been schoolmates in Gloucestershire and remained lifelong friends. Parry received his medical degree from Edinburgh in 1778, and established a successful clinical practice in the ancient city of Bath, legendary for its mineral waters and revitalized by its striking neoclassical architecture in the Palladian style. Parry summarized 18th century understanding of angina pectoris in a slim volume entitled *An Inquiry into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris* (Fig. 1), published in 1799 but based in part on lectures earlier given before the Gloucestershire Medical Society.[4]

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Parry was a strong advocate of Jenner's observation that a link exists between obstructed coronary arteries and angina pectoris. In his monograph, Parry was among the earliest clinical observers to propose a pathophysiologic basis for effort-related chest pain, extending Jenner's pathologic observations to a dynamic formulation. In patients with obstructive coronary disease, "though a quantity of blood may circulate through the arteries," he explained, "sufficient to nourish the heart, as appears, in some instances, there may probably be less than what is requisite for prompt and vigorous action." This proposal clearly introduced the concept of variability of cardiac energy demand as a critical factor in the production of symptoms in patients with angina pectoris. "Hence," he continued, "though a heart so diseased may be fit for the purposes of common circulation during a state of bodily or mental tranquillity and of health yet otherwise good, yet when an unusual exertion is required its powers may fail under the new and extraordinary demand." Proposal of this concept by Parry stands as a monumental early example of physiologic reasoning about diseases of the heart.

Allan Burns

Parry's emphasis on the excessive myocardial energy demand underlying expression of symptoms in angina pectoris was amplified and extended by Allan Burns 10 years later. The short career of Burns was both remarkable and tragic.[5] Born in Glasgow, he apparently never completed formal medical studies, but in 1797 became a laboratory assistant to his older brother John,

AN

INQUIRY

INTO THE

SYMPTOMS AND CAUSES

OF THE

SYNCOPE ANGINOSA,

COMMONLY CALLED

ANGINA PECTORIS;

ILLUSTRATED BY DISSECTIONS:

BY

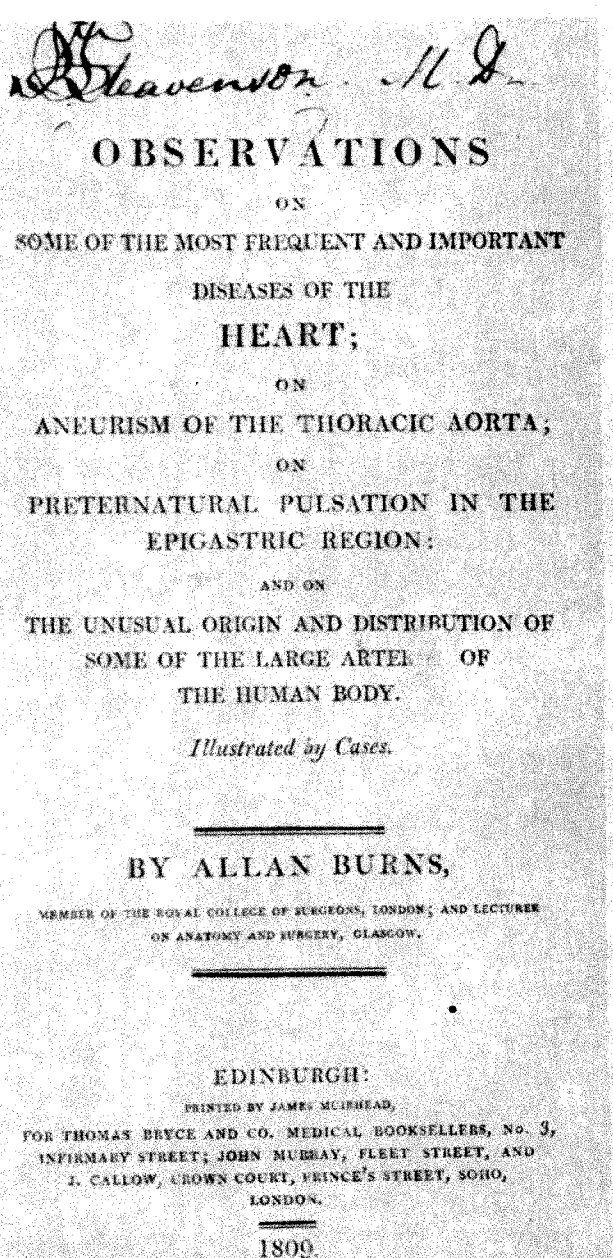
CALEB HILLIER PARRY, M.D.

MEMBER OF THE COLLEGE OF PHYSICIANS OF LONDON, AND OF THE ROYAL MEDICAL SOCIETY OF EDINBURGH; AND ONE OF THE PHYSICIANS OF THE BATH GENERAL HOSPITAL.

BATH, PRINTED BY R. CRUTTWELL;
AND SOLD BY
CADELL AND DAVIES, STRAND, LONDON.

1799.

FIGURE 1. Title page of Parry's *Inquiry*, in which the variability of cardiac energy demand in patients with coronary disease was proposed as a pathophysiologic basis for angina.



OBSERVATIONS

ON

SOME OF THE MOST FREQUENT AND IMPORTANT

DISEASES OF THE

HEART;

ON

ANEURISM OF THE THORACIC AORTA;

ON

PRETERNATURAL PULSATION IN THE EPIGASTRIC REGION:

AND ON

THE UNUSUAL ORIGIN AND DISTRIBUTION OF SOME OF THE LARGE ARTERIES OF THE HUMAN BODY.

Illustrated by Cases.

BY ALLAN BURNS,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS, LONDON; AND LECTURER ON ANATOMY AND SURGERY, GLASGOW.

EDINBURGH:

PRINTED BY JAMES MUIRHEAD,

FOR THOMAS BRYCE AND CO. MEDICAL BOOKSELLERS, No. 3, INFIRMARY STREET; JOHN MURRAY, FLEET STREET, AND J. CALLOW, CROWN COURT, PRINCE'S STREET, SOHO, LONDON.

1809.

FIGURE 2. Title page of Burns's *Observations*, the first comprehensive treatise on heart disease in English.

a prominent Scottish anatomist and demonstrator best known for his work in obstetrics. Despite his lack of formal education, Allan Burns soon established an independent reputation as an anatomist and surgeon, which led in 1804 to an invitation from Catherine of Russia to travel to St. Petersburg to establish and direct a hospital run along Western European lines. This intriguing and prestigious assignment was held for only 6 months, since Burns was obliged to return to Scotland to take over his brother's lecture schedule after John was convicted of body snatching to secure material for his demonstrations. Burns's obligation to his brother may well have been more academic than financial since John, although as a penalty forbidden to teach anatomy, was otherwise allowed to continue his thriving clinical practice of surgery.

Within several years, Allan Burns produced the first comprehensive treatise on cardiology in English, published in 1809 and entitled *Observations on Some of the Most Frequent and Important Diseases of the Heart* (Fig. 2).[6] His text on the heart was written 10 years before the introduction of the stethoscope, and gave careful clinical and pathologic observations on congenital, hypertrophic, and ischemic disease. Burns died of a ruptured appendix 4 years later, at the age of only 32.

Extending Parry's prior work, Burns highlighted the significance of energy supply and demand imbalance in the heart as the pathophysiologic basis for angina pectoris by proposing an experimental analogy that could be verified easily by all clinicians. "If we call into vigorous action a limb round which we have with a moderate degree of tightness applied a ligature," he suggested, "we find then that the member can only support its actions for a very short time; for now its supply of energy and its expenditure do not balance each other; consequently it soon, from its deficiency of nervous influence and arterial blood, fails and sinks into a state of quiescence." Given this easily observed situation of experimental claudication, Burns was then able to formulate an explanation of the origin of anginal pain in patients with diseased coronary arteries. "A heart," he continued, "the coronary arteries of which are cartilagenous or ossified can, like the limb, discharge its functions so long as its action is moderate and equal. When, therefore, the coronary arteries are ossified every agent capable of increasing the action of the heart, such as exercise, passion, and ardent spirits, must be a source of danger."

Historical Development

As occurs with many diseases, the early appreciation of angina pectoris can therefore be seen to have emerged through several discrete stages at the end of the 18th century. The recognition and clinical description of angina are due to Heberden. This was followed by postmortem correlation with coronary artery disease by Jenner, whose work was intimately entwined with that of Hunter, who in turn was both observer and victim of the disorder. And finally, Parry and Burns formulated an understanding of ischemic heart disease as a dynamic imbalance of myocardial energy supply and demand. Their observations stand as brilliant early examples of pathophysiologic reasoning and form the basis of our traditional understanding of effort-related chest pain in obstructive coronary artery disease.

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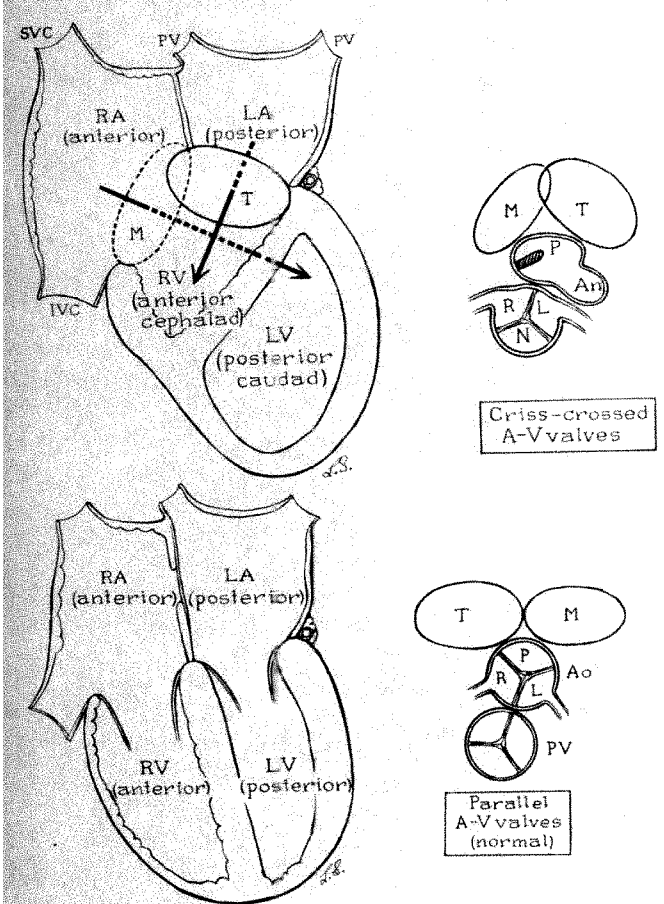
Crisscrossed Atrioventricular Valves and Prolonged Survival

WILLIAM C. ROBERTS, MD, THOMAS L. SPRAY, MD, RICHARD J. SHEMIN, MD, and BARRY J. MARON, MD

Normally, of course, the atrioventricular (AV) cardiac valves have a right-to-left relationship with one another (Fig. 1). The right-sided AV valve connects the right-sided atrium to the right-sided ventricle, and the left-sided AV valve connects the left-sided atrium to the left-sided ventricle. In rare cases, however, the AV valves are not parallel to one another but are crisscrossed, so that the right-sided atrium connects to the left-sided ventricle and the left-sided atrium connects to the right-sided ventricle (Fig. 1). When this occurs, the AV valves have an anteroposterior relation. Since 1974, a number of patients with crisscrossed AV valves have been reported on, and most died early in life from either inadequate or excessive pulmonary blood flow,



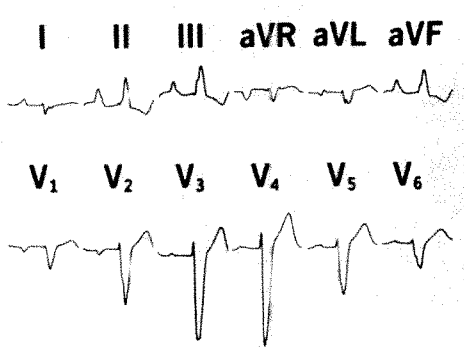


FIGURE 1, left. Diagram showing basic arrangement of the patient's crisscrossed heart (**top**) compared with the normal heart (**bottom**). The valves shown **on the right** are as they appeared after removing the aorta (Ao), pulmonary trunk, and walls of the right atrium (RA) and left atrium (LA). The ventricular septum in the crisscrossed heart is relatively perpendicular to the atrial septum, and this feature allows the crisscrossed valve arrangement. Blood traversing the tricuspid (T) valve from the posteriorly located LA flows anteriorly to the anteriorly located right ventricle (RV) and blood traversing the mitral (M) valve flows posteriorly to the posteriorly located left ventricle (LV). The pulmonic valve (P) (**top only**) is unicuspid and unicommissural, and an aneurysm (An) of its sinus protrudes anteriorly. L = left; N = noncoronary cusp or sinus; P = posterior sinuses of Valsalva of the aortic valve; R = right.

FIGURE 2, top. Electrocardiogram showing intermittent second-degree heart block, left bundle branch block, a P-R interval of 0.21 second, and lack of development of a significant r wave in the precordial leads. V leads ½ standard.

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the latter by way of an associated large ventricular septal defect. This report was prompted by studying a man who lived 55 years with crisscrossed AV valves associated with double outlet right ventricle and pulmonic valve stenosis.

Although cyanosis and a precordial murmur were present at birth and throughout life, the patient was asymptomatic except on extreme exertion until age 46 years when syncope occurred; cardiac catheterization was performed, and operation refused. At age 54 years (10 months before death), 2,500 ml of blood was removed because of a hematocrit level of about 65%. Two months later, diplopia, a sixth nerve palsy, and intermittent Mobitz II heart block with a left bundle branch block pattern appeared, and cardiac catheterization was repeated. The pressures (in mm Hg) were as follows: pulmonary artery, 15/7; right ventricular outflow, 60/10, and inflow, 135/7; right atrial mean, 5; pulmonary artery wedge mean, 7; left ventricle, 125/10; and aorta, 125/71. Examination 4 months before death disclosed a grade 3/6 precordial systolic murmur with thrill, most prominent at the left sternal border. The electrocardiogram, chest

FIGURE 3. Posteroanterior radiograph (**left**) and lateral angiogram (**right**). The aorta (Ao) arises anterior to the stenotic pulmonic valve. LV = left ventricle; PT = pulmonary trunk; RV = right ventricle.

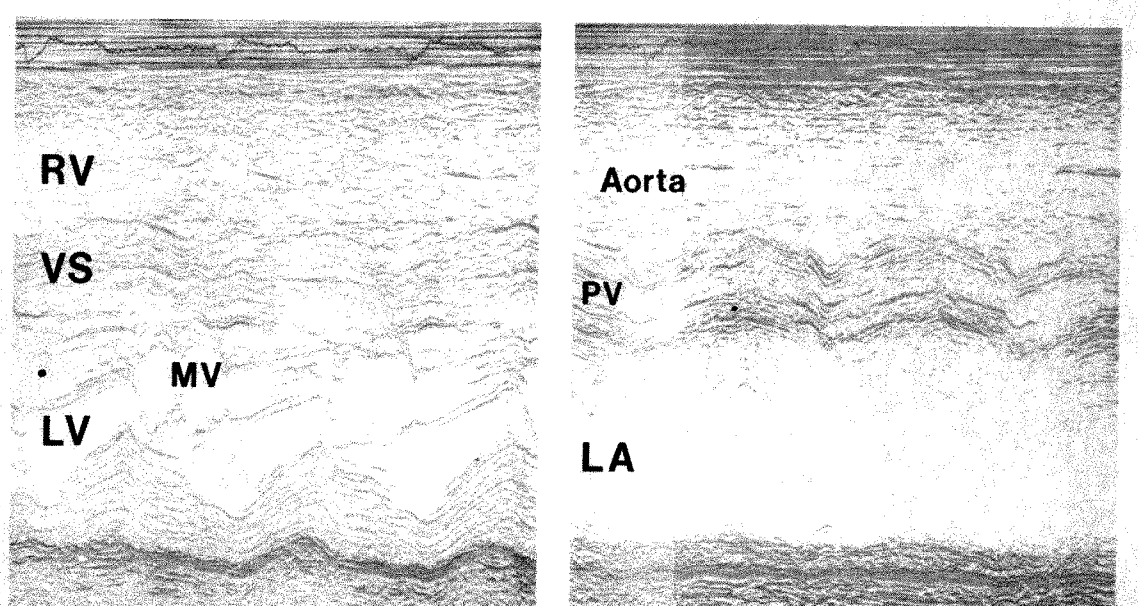

FIGURE 4. M-mode echocardiogram interpreted retrospectively showing (**left**) the mitral valve (MV) to occupy most of the left ventricular cavity (LV), and (**right**) the calcified pulmonic valve (PV) located anterior to the dilated left atrium (LA) and posterior to the aorta. RV = right ventricular cavity; VS = ventricular septum.

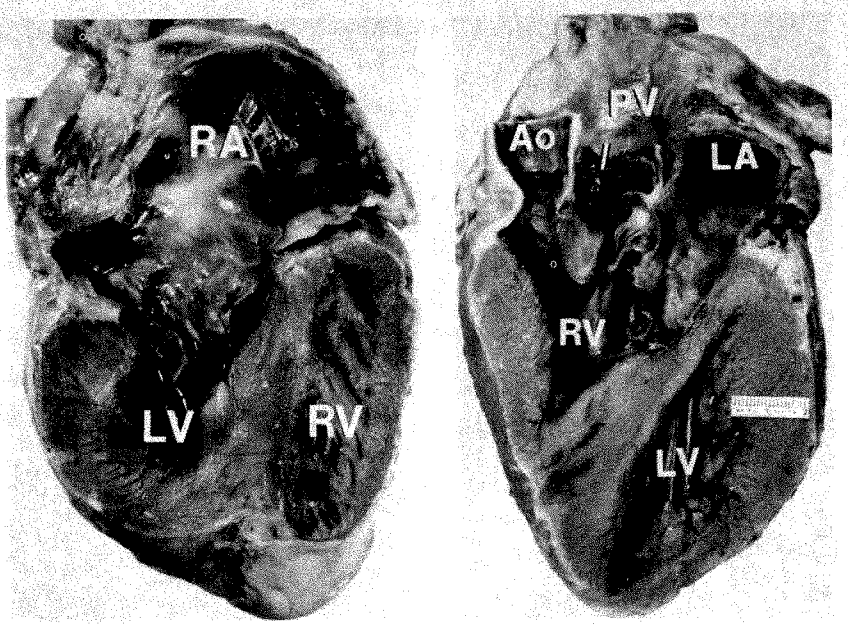

FIGURE 5. Anteroposterior cut of the heart showing (**left**) the right atrium (RA) draining into the left ventricle (LV) and (**right**) the left atrium (LA) draining directly into the right ventricle (RV). Both the aorta (Ao) and the pulmonary trunk arise from the right ventricle. The tricuspid valve is displaced toward the right ventricle, and its leaflets partly obstruct the ventricular septal defect. The conus is inverted. PV = stenotic pulmonic valve.

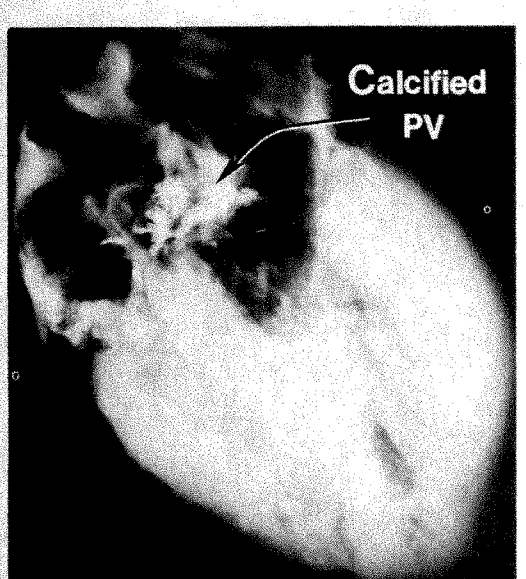

FIGURE 6. Radiograph of heart specimen disclosing heavy calcific deposits in the stenotic pulmonic valve (PV).

roentgenograms, and M-mode echocardiogram are shown in Figures 2 to 4. The right subclavian artery was anastomosed to the right pulmonary artery 70 days before death. Immediately after operation, intractable congestive heart failure developed and 6 days later the Blalock-Taussig shunt was closed; his condition improved briefly, but gradually evidence of poor perfusion of the kidneys, heart, and brain developed and the patient died.

The findings at necropsy are summarized in Figures 1, 5, and 6. The mitral valve, located posterior to the tricuspid

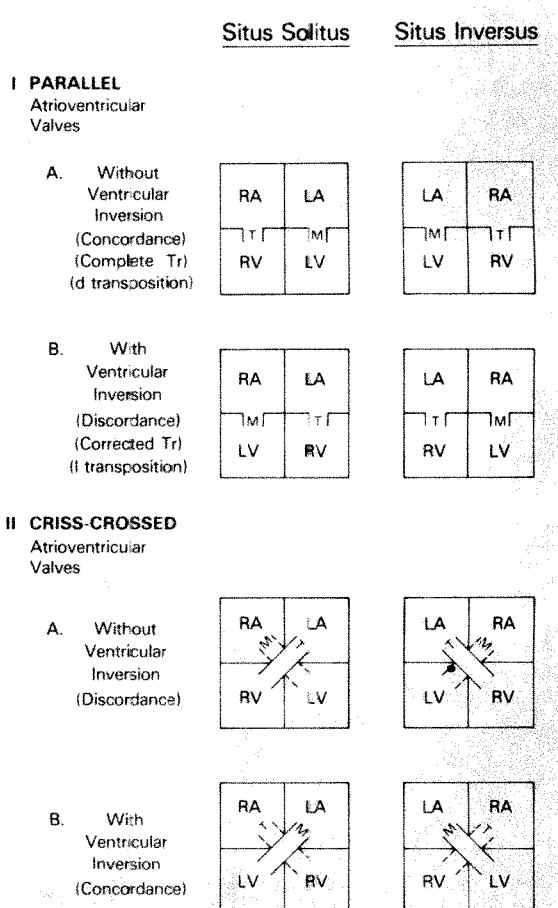

FIGURE 7. Transposition (Tr) of aorta and pulmonary trunk. A proposed classification of transposition complexes including both parallel and crisscrossed AV valves. Abbreviations as before.

valve, connected the right-sided anatomic right atrium to the left-sided anatomic left ventricle, and the tricuspid valve, located anterior to the mitral valve, connected the left-sided anatomic left atrium to the right-sided anatomic right ventricle. The only outlet for blood from the left ventricle was a ventricular septal defect. Both aorta and pulmonary trunk arose from the right ventricle. The pulmonic valve was severely stenotic and heavily calcified (Fig. 6), and a portion of its sinus wall protruded anteriorly (Fig. 1).

This case is by far the oldest reported thus far with crisscrossed AV valves. Of the other 9 necropsy cases reported,[1-6] 4 ([1][Case 13],[2,5][Case 2],[6][Case 7]) died during the first 2 months of life, 1 at 4 years,[3] 2 at 8 years ([1][Case 12],[4]), 1 at 23 years ([6][Case 5]) and 1 at 25 years ([5][Case 1]). Both of the 2 reported patients living longer than 20 years and our patient had obstruction to pulmonary blood flow, a near necessity for prolonged survival with transposition of the great arteries and ventricular septal defect or double-outlet right ventricle.

Nearly all patients with crisscrossed AV valves have malformed or transposed great arteries, the most common being complete transposition and double-outlet right ventricle. Because most present classifications of the transposition complexes assume that the relation of the AV valves to one another is parallel, it is important to delineate this relationship as parallel or crisscrossed because this factor affects intracardiac blood flow and operative therapy[7] (Figure 7).

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N-Acetyl Procainamide Causing Torsades de Pointes

BRIAN OLSHANSKY, MD, JAMES MARTINS, MD, and SCOTT HUNT, MD

Torsades de pointes, a distinctive form of ventricular tachycardia (VT) associated with Q-T prolongation,[1] may be caused by antiarrhythmic agents, particularly quinidine. N-acetyl procainamide (NAPA) has not been reported to cause torsades de pointes, but such appears the case in the patient described herein.

A 74-year-old white woman presented with episodes of recurrent VT associated with syncope. At age 69 years (1977) she was treated unsuccessfully for VT with syncope with quinidine gluconate and disopyramide. Cardiac catheterization at the time showed no significant abnormality. In February 1982 all medications were stopped except hydrochlorathiazide (50 mg/day) for systemic hypertension. Monitoring for 1 week demonstrated no arrhythmia. An electrocardiogram showed left-axis deviation and an echocardiogram demonstrated left ventricular hypertrophy. The ejection fraction was 51% by radionuclide angiography. The serum creatinine level was 2.5 mg/dl and the creatinine clearance rate 28 ml/min.

Programmed right ventricular stimulation from 3 sites at 2 basic cycle lengths with 1 and 2 premature stimuli or right ventricular burst pacing did not induce VT. Left ventricular stimulation produced uniform VT with a left bundle branch block, right axis morphology, at a cycle length of 250 ms; this persisted up to 45 seconds and then stopped spontaneously. VT similar to that induced by pacing occurred after 1 dose of oral procainamide (Procan SR) therapy started on February 26. Additional procainamide administered intravenously prevented recurrence of VT associated with plasma levels shown in Table I. On chronic oral procainamide therapy, no further spontaneous VT occurred, but 1 week later VT was still inducible by left ventricular pacing. After an additional 500 mg of procainamide intravenously, however, VT was not inducible with the same pacing protocols (Table I).

On March 5 she was discharged on procainamide, 1,750 mg orally every 6 hours (Table I). On March 11, she returned with frequent episodes of torsades de pointes (Fig. 1) and a markedly longer Q-T interval. Procainamide was discon-

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TABLE I Sequential Procainamide (PCA) and N-Acetyl Procainamide Levels

Date	PCA Level (μg/ml)	NAPA Level (μg/ml)	Q-Tc (s)	Condition*
2/26	10.2	15.9	0.39	VT stopped
3/1	7.6	25.2	0.44	VT induced
3/1	10.8	26.7	0.44	VT not induced†
3/5	12.5	28.8	0.40	No VT
3/11	11.1	28.7	0.64	Torsades de pointes
3/11	10.2	30.9	0.64	Torsades de pointes
3/12	4.1	32.8	0.61	Torsades de pointes
3/13	1.1	12.4	0.40	No torsades de pointes or VT

* Condition of the patient when drug level was obtained. † After 500 mg of PCA intravenously.

tinued. Isoproterenol infusion at 1 to 3 μg/min prevented torsades de pointes. About 24 hours later, the apparent Q-T interval remained long (Fig. 2) and torsades de pointes recurred when isoproterenol was stopped. The procainamide level had fallen to levels which previously caused no torsades de pointes, but the NAPA level was still elevated (Table I). The next day when the NAPA level fell, isoproterenol was discontinued without torsades de pointes. The patient was subsequently treated with a combination of diphenylhydantoin (serum concentration 15.4 μg/ml) and quinidine, 300 mg orally every 6 hours (trough serum concentration 2.0 μg/ml) and has had no further episodes of syncope, torsades de pointes, spontaneous VT, or pacing-induced VT. The Q-T interval on diphenylhydantoin and quinidine was normal and she has remained asymptomatic on follow-up.

N-acetyl procainamide, a metabolite of procainamide produced by the liver, has antiarrhythmic potency independent of procainamide.[2-4] Kluger et al[3] reported long-term antiarrhythmic therapy with NAPA. Sudden death occurred in 4 of their patients who had peak NAPA levels ranging from 15 to 66 μg/ml. Although NAPA may prolong repolarization and refractoriness,[4] there has been no proof that it produces arrhythmias or torsades de pointes. The long Q-T intervals and the large U waves associated with high NAPA levels may indicate temporal dispersion of repolarization.

It is possible that a high concentration of PCA or a combination of PCA and NAPA caused the torsades de pointes in our patient. Strasberg et al[5] reported that oral or intravenous procainamide was associated with torsades de pointes. In their patients, VT occurred after administration of 200 to 400 mg intravenously or 3 to 4 g orally per day. No blood levels of either procainamide or NAPA were reported. Our patient had torsades de pointes with a serum NAPA concentration of 32.8 μg/ml and a procainamide concentration of 4.1 μg/ml. In our patient, higher serum procainamide concentrations of 10.2 to 12.5 μg/ml alone or higher total NAPA and procainamide concentrations (Table I) were not associated with torsades de pointes. It is highly unlikely that effects of procainamide lagged behind the

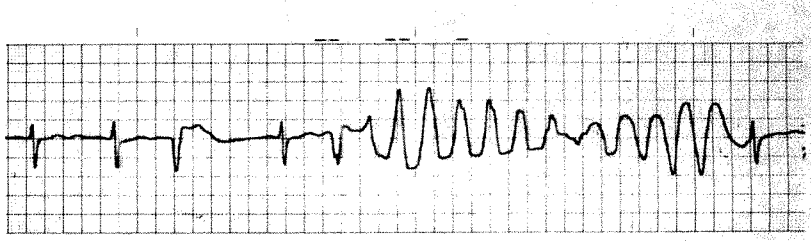

FIGURE 1. Rhythm strip recorded on March 12, 1982 demonstrating a typical episode of spontaneous torsades de pointes which occurred when isoproterenol was stopped. The procainamide level was 4.1 μg/ml and the NAPA level 32.8 μg/ml.

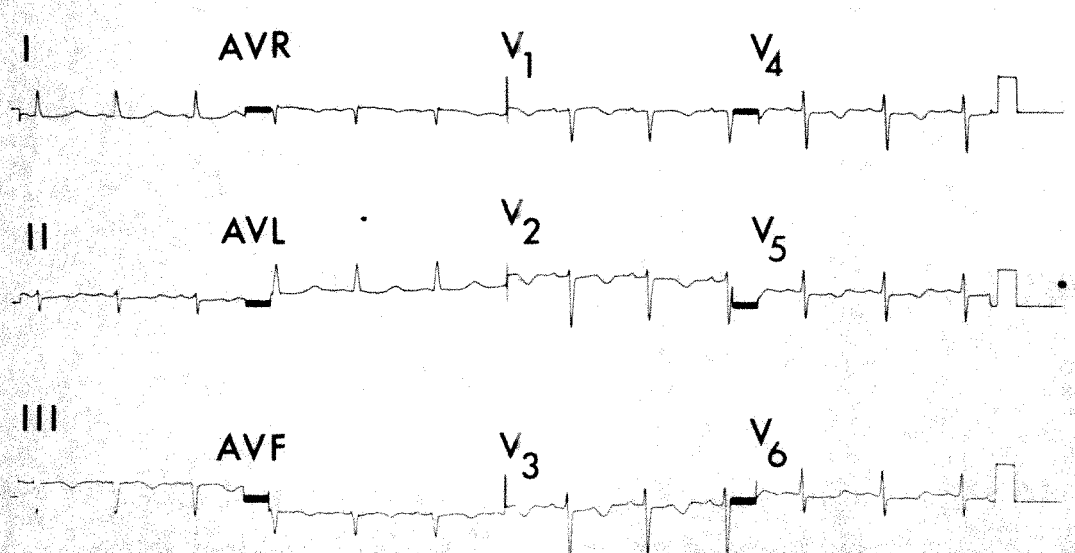

FIGURE 2. Electrocardiogram taken on March 12, 1982 when the procainamide level was 32.8 μg/ml and during isoproterenol infusion, 1 μg/min. Note the long Q-T interval, which may be a fusion of T and U waves, demonstrated best in leads V_4 and V_5.

serum level, particularly since it is reported that arrhythmias in cases of procainamide-induced torsades de pointes cease rapidly after stopping administration of the drug.[5] Therefore, we suggest that the elevated NAPA level was the major cause. In addition, torsades de pointes in our patient was clearly related to serum concentration and was not idiosyncratic.

Thus, elevated NAPA levels may cause torsades de pointes in a patient taking procainamide. Prompt cessation of the drug and temporary isoproterenol therapy or overdrive pacing may be lifesaving.

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Extreme Protective Action of Coronary Collateral Vessels In Complete Occlusion of the Left Main Coronary Artery

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The functional significance of the coronary collateral circulation and its role in preserving left ventricular function has been the subject of considerable controversy.[1,2] The case presented here is an example of coronary collaterals protecting virtually all the left ventricular myocardium.

A 52-year-old man had had angina pectoris for 2 years. During the 2 weeks before cardiac catheterization, the frequency and severity of the anginal episodes increased dramatically. Findings on physical examination were unremarkable. Electrocardiograms are shown in Figure 1. At coronary angiography, the left main coronary artery was totally occluded (Fig. 2) and the right coronary artery was narrowed up to 50% in diameter (Fig. 3). The left ventricle was normal on angiography (ejection fraction 65%) (Fig. 4). Aortocoronary grafts were placed to the left anterior descending coronary artery and to the obtuse marginal branch of the left circumflex coronary artery, and 32 months after operation the patient was asymptomatic.

Occlusion of the left main coronary artery, almost invariably associated with left ventricular contraction abnormalities, has been reported by several investigators.[3–5] While rare cases of normal left ventricular function in the presence of a totally occluded left main coronary artery have been reported,[5,6] the association of total left main coronary occlusion, nondominant right coronary artery, and normal left ventricular function

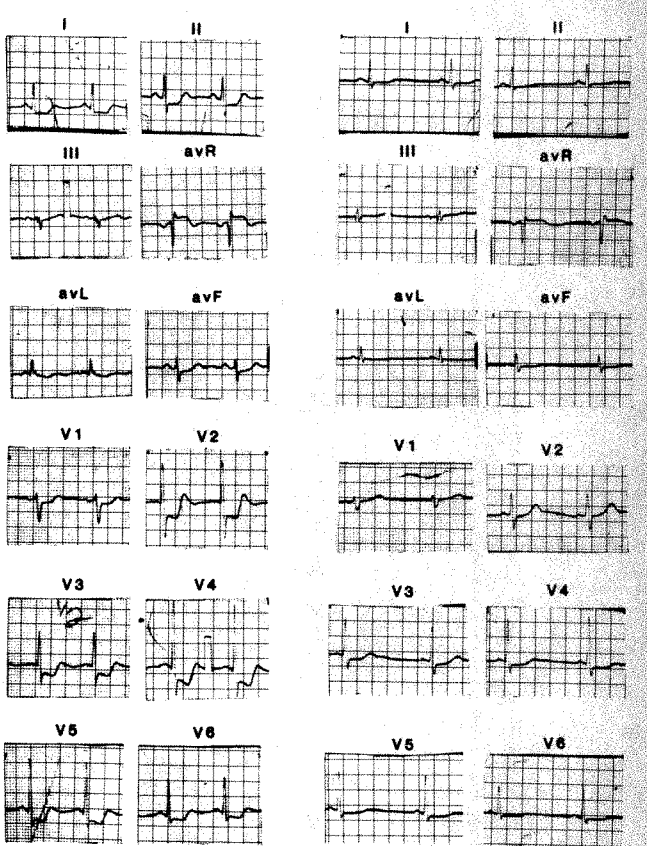

FIGURE 1. Twelve lead electrocardiogram taken shortly after anginal episode (**left**) and before catheterization (**right**).

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FIGURE 2. Visualization of the left main coronary artery, occluded about 5 mm from the ostium.

FIGURE 3. Visualization of the right coronary artery in the right anterior oblique projection. Several atrial and right ventricular branches originate from the right coronary artery, which is about 50% obstructed (**arrow**). Rich intercoronary collaterals afford visualization of the left anterior descending and the circumflex coronary artery and their branches. The posterior descending branch is given by the circumflex. 1 = right coronary artery; 2 = left anterior descending; 3 = major diagonal branch; 4 = septal branches; 5 = circumflex; 6 = posterior descending.

has not been described previously. The development of adequate coronary collateral vessels is capable of preserving left ventricular function even when the left main coronary artery is totally occluded.

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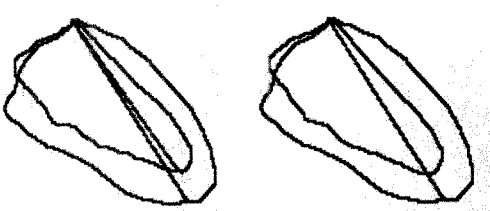

FIGURE 4. Computer-generated plots of the left ventricular end-systolic and end-diastolic contours. **Left,** end-systole unshifted; **right,** end-systole shifted.

Percutaneous Balloon Valvuloplasty for Pulmonic Valve Stenosis in the Adult

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The management of pulmonic valve stenosis (PS) by surgery is very effective. The recent success of transluminal balloon angioplasty as an alternative to coronary bypass or vascular surgery prompted the application of this principle to a *child* with moderate PS.[1] The early and 4-month follow-up suggested that effective dilatation had been achieved. We performed percutaneous balloon valvuloplasty in an *adult* with severe PS.

A 59-year-old woman who had had a precordial murmur since early childhood did well until approximately 1 year before admission, when fatigue and exertional dyspnea began to markedly limit her activities. She had had vague, probably nonischemic chest pain for several years.

Blood pressure was 160/90 mm Hg, and the pulse rate 80 beats/min and regular. She weighed 245 pounds and stood 60 inches tall. She had a prominent parasternal impulse. A loud pulmonic ejection click was heard at the left sternal border. The S_2 sound was split widely, and a prominent

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TABLE I Hemodynamic Findings

	Before Valvuloplasty	Immediately After Valvuloplasty	10 Days After Valvuloplasty
HR	78	80	68
RA	A = 20(15)	A = 12(9)	A = 10(6)
RV_B	160/17	97/10	68/8
RV_I	160/17	65/10	68/8
PA	20/14(18)	23/13(18)	30/15(18)
PAW	(14)	. . .	(15)
LA	(14)	. . .	(13)
SA	160/85(115)	142/75(100)	166/80(114)
CO	4.9	. . .	5.2
A-VO_2 diff	26%	. . .	28%
PVG	(130)	. . .	(30)
PVA	0.3	. . .	1.0

Values in parentheses are mean values. AVO_2 diff = arterial-mixed venous oxygen saturation; CO = cardiac output (liters/min); HR = heart rate (beats/min); LA = left atrial pressure (mm Hg); PA = pulmonary artery pressure (mm Hg); PAW = pulmonary artery wedge pressure (mm Hg); PVA = effective pulmonic valve area (cm^2); PVG = pulmonic valve pressure gradient (mm Hg); RA = right atrial pressure (mm Hg); RV_B = right ventricular body pressure (mm Hg); RV_I = right ventricular infundibular pressure (mm Hg).

systolic thrill was present at the second left sternal border. A grade 4/6 systolic ejection murmur was present. No diastolic murmur was detected. There was no cyanosis, clubbing, or edema.

Electrocardiography showed sinus rhythm with a mean electrical axis of 120°. The R/S ratio in lead V_1 was >1. There were nonspecific ST-T wave changes in the precordial leads. The P wave was prominent in leads II, III, and aVF. Radiography of the chest disclosed cardiac enlargement with a right ventricular prominence. No calcium was present in the pulmonic valve area. Both the pulmonary trunk and left main pulmonary artery were markedly dilated. The hemodynamic findings are summarized in Table I.

During a Valsalva maneuver, injection of indocyanine green into the inferior vena cava disclosed a small right-to-left shunt. A catheter patent foramen ovale was present. Left ventricular cineangiography demonstrated a normal-sized left ventricular cavity and ejection fraction and no regional wall motion abnormalities. Selective coronary angiography showed normal coronary arteries. On right ventricular cineangiography the obstruction appeared limited to the pulmonic valve, which "domed" in systole and "inverted" in diastole. The cusps were thickened but not calcified. Direct measurements from the projected cineangiographic frame revealed the systolic diameter of the pulmonic valve "ring" to be 2.0 cm.

Catheter Design

Based on direct measurements of the valve ring, a catheter was fabricated (Meditech, Watertown, Massachusetts) for use in the pulmonic valve. The catheter was 9 French with a tapered tip and end hole and contained a 20 × 40 mm polyethylene balloon. When inflated by hand at 5 atmospheres of pressure with 10 ml of 50% Renografin® and 50% saline solution, the time from onset of inflation to 90% deflation averaged 8 seconds. Since the distal end of the catheter was tapered for percutaneous introduction and was relatively rigid, the catheter was made for use over an 0.038-inch guidewire to ensure protection of the pulmonary artery.

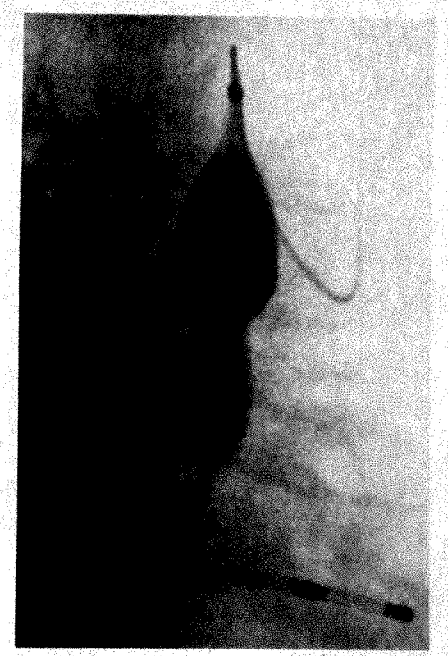

FIGURE 1. Position of the balloon, centered across the stenotic pulmonic valve early during the initial inflation. "Hourglass" configuration of the contrast-filled balloon is created by the stenotic valve. The 0.038-inch J guidewire is in the left main pulmonary artery. After this inflation no reduction in right ventricular systolic pressure occurred (see Figure 2).

Catheter Insertion and Valvuloplasty Technique

Diphenhydramine (50 mg), heparin (5,000 units), and atropine (0.4 mg) were administered. The balloon catheter was inserted without a sheath into the right femoral vein over a 0.038-inch exchange guidewire. This wire had previously been positioned in the left main pulmonary artery using another catheter. Under fluoroscopic and electrocardiographic monitoring, the balloon catheter was advanced to the pulmonic valve region. The location of the balloon was adjusted so that it was positioned across the pulmonic valve. The guidewire was left in place to help stabilize the balloon during inflation and provide a rapid and safe pathway for balloon advancement should hemodynamic deterioration occur during inflation. Right ventricular pressure was monitored from a site below the valve using another catheter. Systemic pressure was monitored from a 5 French catheter inserted percutaneously.

Valvuloplasty was done with constant electrocardiographic, hemodynamic, and fluoroscopic monitoring. The balloon was inflated by hand syringe with 10 ml of 50% Renografin and 50% saline solution. With the initial inflation to 8 ml an indentation, caused by the stenotic valve, was seen (Fig. 1). During inflation there was an increase in right ventricular pressure and a decrease in systemic pressure. Right ventricular and systemic pressures were restored within 6 to 8 seconds after deflation (Fig. 2). After the initial inflation, there was no decrease in right ventricular pressure. This "hourglass" appearance disappeared when the balloon was inflated with 10 ml at 5 atmospheres and the balloon filled

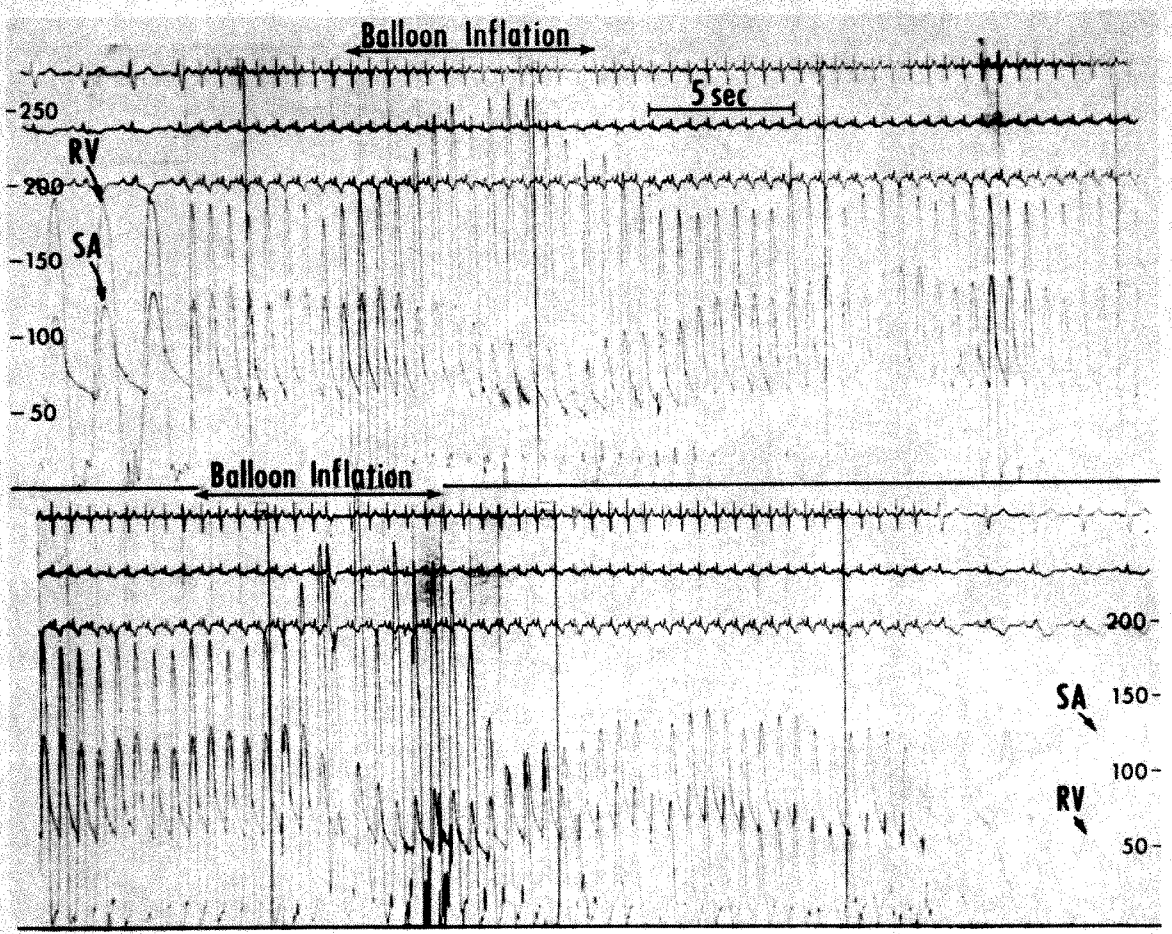

FIGURE 2. Right ventricular (RV) and systemic (SA) arterial pressure recordings before, during, and after balloon inflation. Electrocardiographic leads I, II, and III are shown from top to bottom. **Upper panel,** recordings during initial balloon inflation shown in Figure 1. There was an increase in peak systolic right ventricular pressure and a decrease in systemic arterial pressure as the heart rate increased only slightly. When the balloon was deflated, right ventricular systolic pressure and systemic pressure returned to preinflation values. **Lower panel,** continuous recordings during another inflation-deflation cycle again show elevation of right ventricular pressure with a decrease in systemic pressure. This inflation was associated with a premature ventricular contraction. The balloon distended fully as the indentation from the stenotic valve disappeared (Fig. 3). Shortly after balloon deflation, right ventricular systolic pressure decreased to 68 mm Hg.

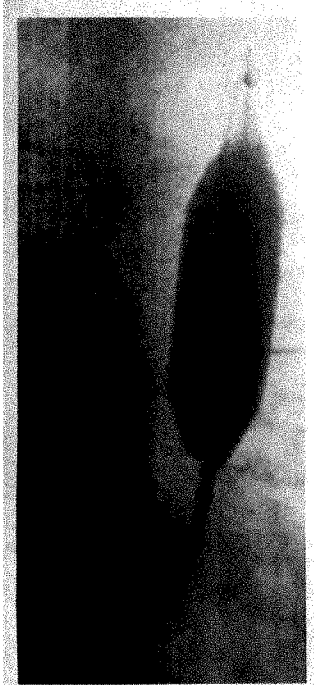

FIGURE 3. Full inflation of the balloon to a diameter of 2 cm.

completely (Fig. 3). This time when the balloon inflated, the increase in right ventricular pressure was associated with premature ventricular contractions (Fig. 2). The patient complained of a fullness in the chest. With deflation, there was a prompt decrease in right ventricular pressure. On pull-back of the pressure monitoring catheter from the subvalvular region, an infundibular pressure gradient was consistently recorded (Table I). For this reason, additional inflations were not performed and the balloon catheter was removed.

Immediately after dilatation there was marked reduction in the intensity of the systolic murmur. The thrill was no longer palpable and the pulmonic ejection sound disappeared. No pulmonic diastolic murmur was heard. She did well and was discharged from the hospital 2 days later. One week after dilatation, she reported marked improvement in effort tolerance. Repeat catheterization studies 10 days after dilatation disclosed disappearance of the infundibular pressure gradient, and right ventricular systolic pressure was 68 mm Hg. The pulmonary artery pressure tracing had a normal configuration. The effective valve area was 1.0 cm^2 (assuming no regurgitation). Right ventricular cinean-

giography showed no infundibular obstruction, and the pulmonic valve orifice increased. No evidence for pulmonic regurgitation was present.

Comments

The potential for right to left shunting through a catheter patent foramen ovale probably helped avoid the profound systolic hypotension and bradycardia during balloon obstruction of the valve orifice, described in the child recently reported.[1] Immediately after relief of valvular obstruction, an infundibular pressure gradient developed in our patient. This is probably analogous to infundibular obstruction often described after surgical valvulotomy for pulmonary stenosis, which generally regresses.[2,3] In our patient infundibular obstruction regressed 10 days after balloon valvuloplasty, and no additional problems were identified.

Acknowledgment: We are indebted to Josh Tolkoff (Meditech) for excellent technical help and fabrication of the catheter, to Robert I. White, MD, for valuable suggestions, to Tom Sollaway, and to the Cardiac Fellows of the University of Florida, Gainesville, Florida.

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EFFECTS OF ATRIAL EXTRASTIMULATION AND RAPID PACING ON ATRIAL FLUTTER CYCLE

The excellent report of Inoue et al[1] prompts comments on the mechanism of atrial flutter (AF) in humans. Studying the effects of programmed atrial stimulation on common AF cycle in man, we observed that the poststimulation cycle, recorded at stimulation point, was equal to the basic AF cycle in some patients,[2,3] suggesting that reentry is its electrogenetic mechanism.

Recently we studied 13 patients[4] during episodes of spontaneous common AF with simultaneous multiple atrial endocardial recordings and atrial programmed stimulation. All patients had 1 catheter positioned in the low paraseptal atrium and another in the high right atrium. The 2 sites were named point 1 and point 2, respectively. In all patients low paraseptal atrial activation (point 1) preceded high right atrial activation (point 2), as already documented.[5,6] By programmed single high right atrial (point 2) stimulation, the following were observed: (a) persistence of AF but with early reset of the cycle; (b) however premature the stimulus was, it never modified the simultaneous atrial activation time at point 1; (c) the pattern of atrial activation in the poststimulation atrial complex remained unchanged; (d) the length of the poststimulation atrial cycle recorded at point 1 (that is, a point reached before the stimulation point by the spreading AF wavefront) was always shorter than both the basic AF cycle length and the poststimulation cycle length recorded at point 2. The diagram in Figure 1 represents 1 of these patients.

The existence of a reentry circuit to which the extrastimulus has access before the head of the circus moving wave explains the fact that high atrium-delivered premature stimuli are followed by a poststimulation low atrial recorded cycle length always less than basic AF cycle length, with the following AF activation pattern remaining unchanged.

These results agree with those of Inoue et al,[1] although obtained with different techniques. Thus, we agree with them that there is good evidence of a reentry as electrogenetic mechanism of spontaneous common AF in humans.

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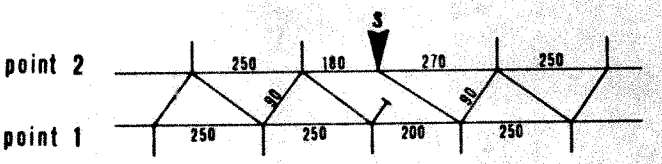

FIGURE 1. Diagram representing 1 of the 13 patients studied.

REPLY: The observations reported by Disertori and Furlanello are identical to those shown in canine atrial flutter (AF).[1] We agree that their observations support the reentry with an excitable gap as the mechanism for human AF.

Some points in their letter deserve comment. First, the phenomenon of the poststimulation cycle being equal to the basic AF cycle does not always support a reentry. As observed by Breithardt et al,[2] if conduction time between the pacing site and the automaticity focus is negligible, the poststimulation cycle might be identical to the basic cycle length. Second, the term *poststimulation cycle* is not appropriate. As shown in the Figure 1, the curtailed cycle on the electrogram of point 1 is a stimulus-encompassing one. Third, in patients with a circus movement turning in the opposite direction, extrastimulation from point 2 may produce a different response, since several factors such as spatial relation between the stimulation site and the recording site,[1] refractory period, and conduction time may modify the effect of extrastimulation.

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Tokyo, Japan

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2. **Breithardt G, Seipel L, Both A, Loogen F.** Direct stimulation of sinus node in man. Eur J Cardiol 1975;3,4:323–328.

ATYPICAL D-TRANSPOSITION OF THE GREAT ARTERIES

We have read with interest the case reported by Marin-Garcia and Edwards[1] as "atypical d-transposition with anterior pulmonary trunk." The authors emphasize the importance of their case to the continuing debate concerning the nomenclature of hearts that, in terms of their ventriculoarterial connections, have ventriculoarterial discordance. It seems to us that their own report is most misleading in this respect when they use the term "d-transposition" to describe generally hearts with atrioventricular concordance and ventriculoarterial discordance, a combination to our minds best described as complete transposition. Indeed, at places in their report, Marin-Garcia and Edwards give us the impression that they consider d-transposition synonymous with complete transposition. But this becomes confusing when they state, "In the registry of Cardiovascular Pathology of United Hospitals–Miller Division there are 234 specimens of d-transposition." Does this mean that there are 234 specimens with ventriculoarterial discordance in which the aorta is right-sided? If so, does this number include examples of corrected transposition

* Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

with situs inversus, in which the aorta is usually d-transposed and, if so, are these justifiably included? Alternatively, does the statement mean that there are 234 specimens with complete transposition? If the latter, does this include examples in which the aorta is directly anterior or left-sided? Perhaps Marin-Garcia and Edwards would describe these cases as "atypical d-transposition with anterior or left-sided aorta"! We submit that "d-transposition" is a most inappropriate synonym for complete transposition if this is in fact intended. This is because it describes what is in essence a "connections malformation" in terms of arterial interrelations. The root of the problems of terminology of transposition has been the failure to distinguish connections from relations.[2]

We also question the interpretation of the morphologic findings, recognizing that this is difficult and indeed, even presumptuous, when we can see only limited photographs. Nonetheless, on the basis of the published illustrations, we suggest that an alternative interpretation is that the pulmonary trunk overrode the anterior ventricular septum, being mostly connected to the right ventricle, and that a more appropriate diagnosis would be double outlet right ventricle. This raises the equally contentious topic of the differentiation of double outlet right ventricle and ventriculoarterial discordance when there is overriding of the pulmonary valve. A significant point in this differentiation is the position of the anterior descending coronary artery. As far as we can judge from Figure 3a, this artery is to the *left* of the pulmonary trunk, suggesting to us that the pulmonary trunk is connected in its greater part to the right ventricle.

Certainly Figure 2 is consistent with the diagnosis of double outlet right ventricle, and Figure 1 does not exclude it since the anterior septum is not profiled. The problem of this type of double outlet right ventricle with sequestration of part of the right ventricle to the left ventricle was recently discussed by Bietzke et al,[3] and their Figure 3 is very similar to Figure 3 of Marin-Garcia and Edwards.[1] The case of Marin-Garcia and Edwards[1] does, of course, have an additional subaortic ventricular septal defect and a subpulmonary infundibulum ("conus").

There is no doubt that the case described by Marin-Garcia and Edwards[1] is closely related to the anomaly of "posterior transposition," this being emphasized by the subaortic defect with mitral-aortic continuity through its roof. However, all previously reported cases of posterior transposition have not had subpulmonary ventricular septal defects and have not had overriding pulmonary valves. The presence of these lesions in this case[1] is further evidence of the "spectrum" of anomalies that exists between double outlet right ventricle and ventriculoarterial discordance.[4] But we submit that the impact of this particular case to the important and ongoing debate concerning nomenclature is blurred by the failure to describe clearly the ventriculoarterial connection and to distinguish it from arterial interrelations.

Gaetano Thiene, MD, Padova, Italy, and
Robert H. Anderson, MD, London, England

1. **Marin-Garcia J, Edwards JE.** Atypical d-transposition of the great arteries: anterior pulmonary trunk. Am J Cardiol 1980;46:507–510.
2. **Macartney FJ, Shinebourne EA, Anderson RH.** Connections, relations, discordance and distortion. Br Heart J 1976;38:323–326.
3. **Beitzke A, Anderson RH, Wilkinson HL, Shinebourne EA.** Two-chambered right ventricle: simulating two-chambered left ventricle. Br Heart J 1979;42:22–26.
4. **Goor DA, Edwards JE.** The spectrum of transposition of the great arteries, with special reference to developmental anatomy of the conus. Circulation 1973;48:406–415.

REPLY: We used d-transposition and complete transposition synonymously, stating in the introduction of our manuscript that "the hallmark of d- or complete transposition of the great arteries is connection of the anteriorly lying aorta with the right ventricle, while the posteriorly lying pulmonary trunk arises from the left ventricle." This definition we believe is simple and descriptive. As we stated, in the Registry of Cardiovascular Pathology of United Hospitals there are 234 specimens of d- or complete transposition, and this series does not include cases of corrected transposition.

Based on our experience and others, our case is not an example of double outlet right ventricle. Clinically, it was considered in the differential diagnosis but at necropsy the aortic and pulmonary orifices originated entirely from the right and the left ventricle, respectively. Indeed, there was a second, small ventricular septal defect located below the subpulmonary conus. Quero Jimenez and Perez Martinez[1] reported a similar case (Case 1) where the anterior portion of a large ventricular septal defect was located below the subpulmonary conus. Moreover, Case 3 of Wilkinson and associates[2] exhibited a small blind-ended sinus below the pulmonary valve. It is possible that the sinus represented a patent, subpulmonary ventricular septal defect at some point pre- or postnatally.

In our case the anterior descending artery arose from the left coronary artery, and its course was anterior and to the right of the pulmonary trunk, a feature that cannot be clearly outlined from the published photographs. In our opinion, our case is similar to those originally reported by Van Praagh and associates[3] and the term atypical d- or complete transposition was coined to describe an unusual situation in simple terms that may be helpful to clinicians and surgeons as well.

José Marin-Garcia, MD, and
Jesse E. Edwards, MD, St. Paul, Minnesota

1. **Quero Jimenez M, Perez Martinez V.** Uncommon conal pathology in complete dextrotransposition of the great arteries with ventricular septal defect. Chest 1974;66:411–417.
2. **Wilkinson JL, Arnold R, Anderson RH, Acerete F.** "Posterior" transposition reconsidered. Br Heart J 1975;37:757–766.
3. **Van Praagh R, Pérez-Treviño C, López-Cuellar M, Baker FW, Zuberbuhler JR, Quero M, Pérez VM, Moreno F, van Praagh S.** Transposition of the great arteries with posterior aorta, anterior pulmonary artery, subpulmonary conus and fibrous continuity between aortic and atrioventricular valves. Am J Cardiol 1971;28:621–631.

PREDICTING CARDIAC MORBIDITY

In their article on predicting cardiac morbidity in patients who have undergone coronary angiography, Dimsdale et al[1] use the statistical technique of stepwise discriminant analysis to select the variables which are most important in separating those patients who experience a cardiac event from those who don't. They indicate that the variables selected are highly significant ($p < 0.00005$ for all patients, $p < 0.0001$ when surgical patients are excluded), and report that the use of these variables in a discriminant function results in a high percentage of patients whose fate is correctly predicted (78% for all patients, 83% when surgical patients are excluded). The use and interpretation of this statistical technique in this situation presents some difficulties.

First, the technique used is based on the assumption that the variables in the analysis follow a multivariate normal distribution. Since most of the variables are dichotomous or categorical in nature, the assumption that they are continuous and from a multivariate normal distribution is far from being met. There are other discriminant analysis models which can be used for categorical data, such as the multivariate logistic model,[2] which are designed to overcome these problems. In practice, however, analyses utilizing logistic discrimination often result in variable selections that are similar, if not identical, to that obtained by the use of ordinary discriminant analysis with discrete variables. For that reason, it is quite

possible that a logistic analysis might identify the same variables as being important.

The interpretation of the results in the article is a bit more troublesome. The emphasis on the small p values and high percentage of correct classification imply that the use of these variables in a prediction equation provides a very accurate method of identifying individual patients who will suffer a cardiac event. In fact, the small p values indicate that the patients who experienced cardiac events have mean values for the variables selected in the analysis which are significantly different (in a statistical sense) from the mean values for patients who did not suffer cardiac events, utilizing a multivariate test. It does not say what the magnitude of those differences are, or if such differences would be very useful in identifying patients prone to suffer a cardiac event. The use of the percentage of patients correctly classified is an attempt at an evaluation of how useful the variables are in identifying patients at risk for future events, but the results quoted suggest that the information learned from the analysis is minimal, if it is interpretable at all. For example, in the analysis including all patients given in Table III, it is indicated that 78% of the patients were correctly classified. However, from Table II, one can see that 75% of the patients did not experience a "morbid event," since an emergency room visit was not counted as such an event. Thus, one could correctly classify 75% of the patients, ignoring all the data, by merely predicting that no one would experience any cardiac events. The use of several variables in a complicated statistical equation results in correctly classifying an additional 3% of the patients, not an impressive result. One could better interpret the results if the sensitivity and specificity of the predictions were also given, to see if the predictions were more accurate among those who did suffer events than in those who did not, but that information is not retrievable from the data published.

Timothy A. DeRouen, PhD,
Seattle, Washington

1. **Dimsdale JE, Gilbert J, Hutter AM, Hackett TP, Block P.** Predicting cardiac morbidity based on risk factors and coronary angiographic findings. Am J Cardiol 1981;47:73–76.
2. **Anderson JA.** Logistic discrimination with medical applications. In: Cacoullos T, ed. Discriminant Analysis and Applications. London: Academic Press, 1973:1–15.

REPLY: DeRouen raises some helpful points regarding the interpretation of our approach for predicting subsequent cardiac morbidity. Our article stresses 2 points: (1) that many variables thought related to the clinical course of heart patients were in fact not found related to subsequent cardiac morbidity, (2) that with discriminate analysis, we were able to derive a weighting of those variables found most helpful in predicting subsquent morbidity. Of the many variables studied, these variables (angina, history of myocardial infarction, family history of heart disease, fatigue, and type A personality) were found to contribute the most information in prognosticating subsequent morbidity.

That this approach is statistically useful in discriminating subsequent morbidity is demonstrated by the high levels of significance of the discriminate analysis (for example, $p < 0.00005$ for all patients). DeRouen asks us to expand on aspects of this work that pertain to its clinical utility. We included as a rough measure of clinical utility the total predictive accuracy for our analysis of all followed subjects (n = 189, total accuracy = 78%) and for subjects who had no surgical intervention (n = 111, total accuracy = 83%).

To discuss further the clinical utility of this approach, we need to consider sensitivity (the extent to which patients with subsequent morbidity are correctly classified) and specificity (the extent to which patients who did not develop morbidity are correctly classified).[1] These concepts refer roughly to the ability of our analysis to accurately "rule in" or "rule out" subsequent morbidity.

For the total sample of 189 patients, the sensitivity was 37% and the specificity 93%. For the medically treated sample, these figures were 48 and 93%, respectively. Thus, our approach would appear useful in ruling out patients for subsequent morbidity but of less use in "ruling in" patients for subsequent morbidity. By adjusting the discriminate function cut point, one could increase sensitivity at the expense of decreased specificity or vice versa. This particular cut point was chosen so that the total predictive accuracy would be maximized.

DeRouen asks in essence, "What's so good about 78% predictive accuracy if I can achieve 75% predictive accuracy merely by predicting that no one will develop morbidity?" The consequence of such a decision-making strategy would be 0% sensitivity; Dr. DeRouen would misclassify *all* of the patients who subsequently had morbidity.

Joel E. Dimsdale, MD, Adolph M. Hutter, MD, Peter C. Block, MD, and Thomas P. Hackett, MD,
Boston, Massachussetts

1. **MacMahon B, Pugh T.** Epidemiology: Principles and Methods. Boston: Little Brown, 1970.

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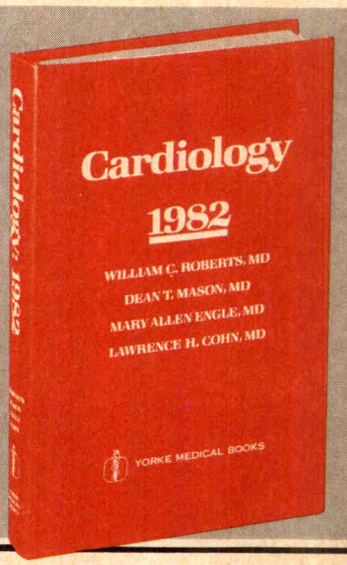

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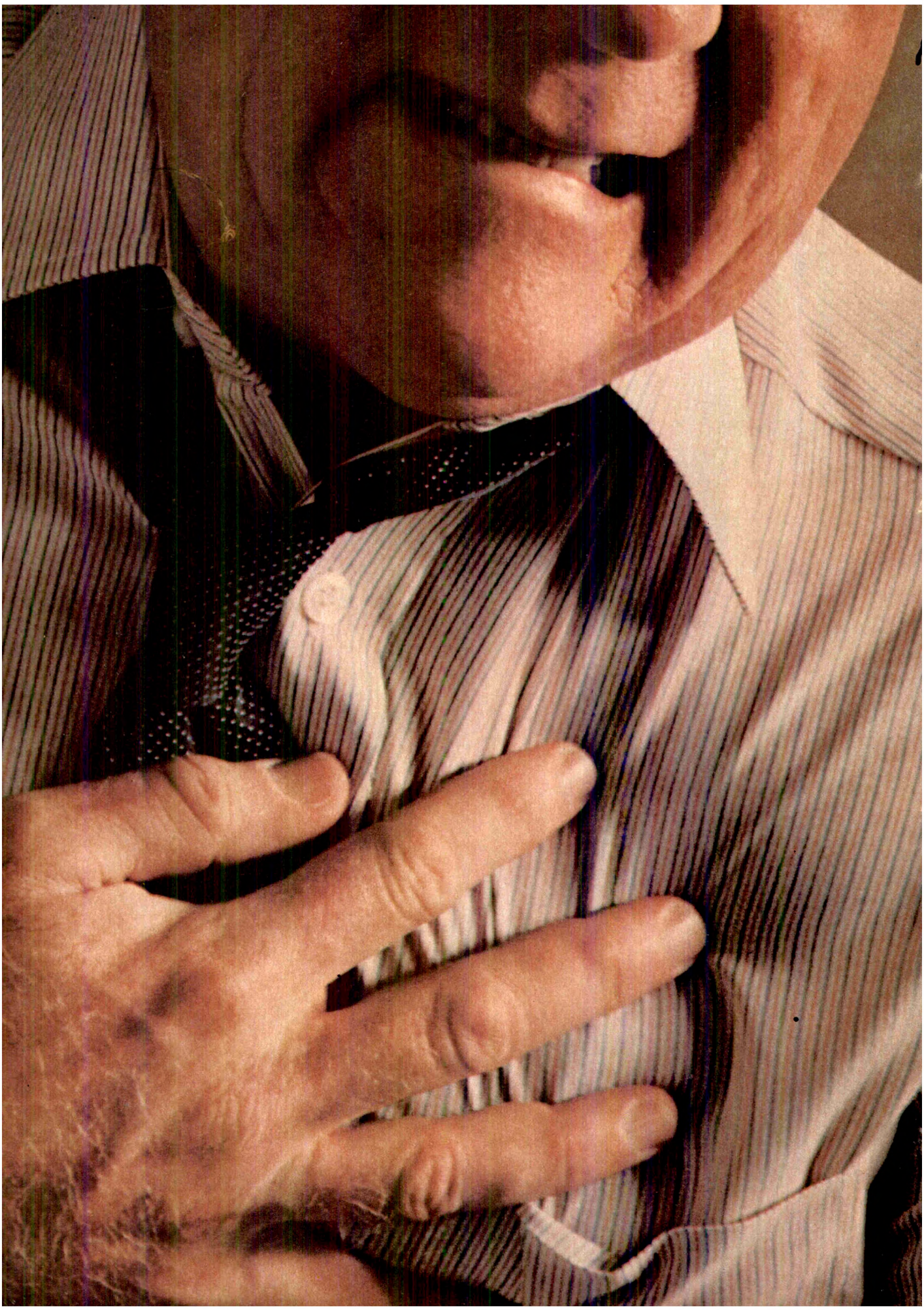

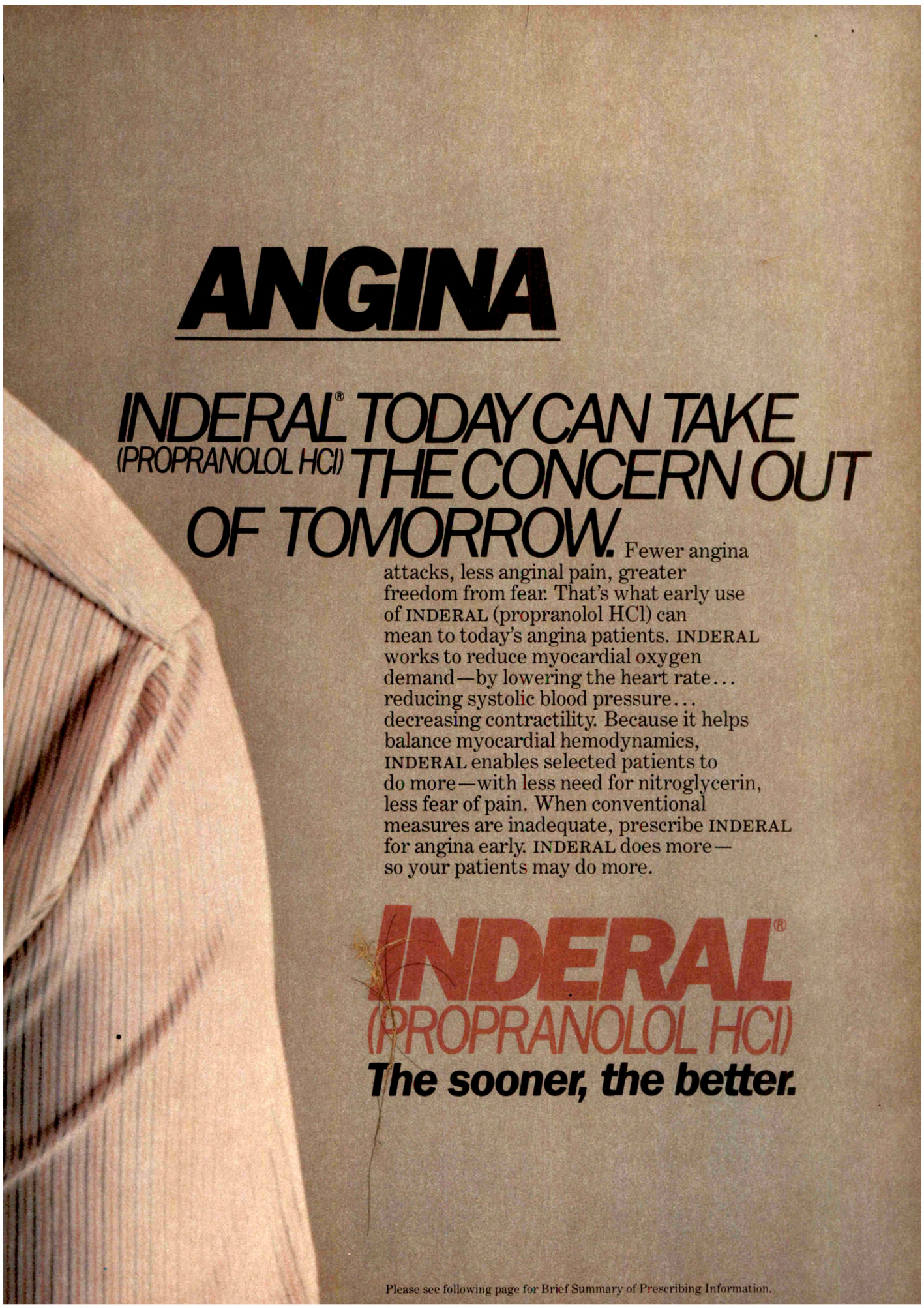
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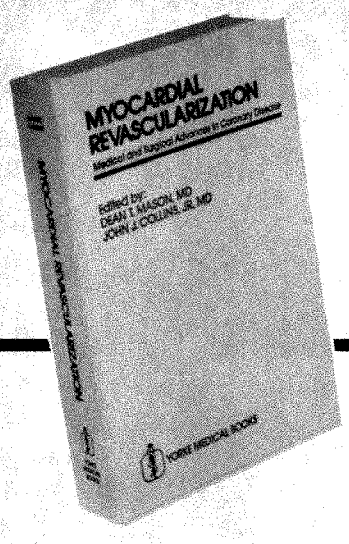

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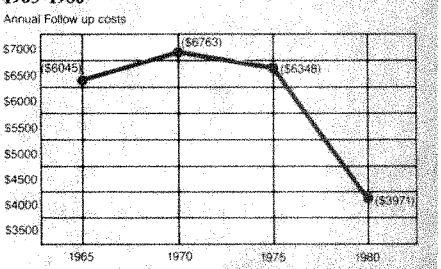
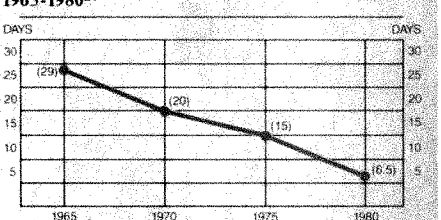


1. Ref. cit. "A Fifteen Year Study of Cardiac Pacing Costs", C. Langer, A. Lopman, S. Furman, D. Escher. *PACE*, May-June, 1981.

DECLINING NUMBER OF HOSPITAL DAYS PER PACEMAKER PATIENT 1965-1980[2].



2. Ref. cit. "A Fifteen Year Study of Cardiac Pacing Costs", C. Langer, A. Lopman, S. Furman, D. Escher. *PACE*, May-June, 1981.

Medtronic

Discover the Medtronic Difference.

Medtronic Implantable Pulse Generators and Leads

Intended Uses

Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses). An atrial pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation disorders but with intact, functioning A-V conduction systems. Cardiac pacing using an implantable A-V sequential pulse generator is for long-term therapeutic control of heart rate in patients where restoration of A-V synchrony is indicated to improve cardiac output or to protect against arrhythmias related to sequence of cardiac impulse propagation.

Contraindications

There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.

Warnings

Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. See the specific precautions and warnings in the technical manuals included with the pulse generator.

Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

for many post-MI patients...

Cardio-protective.

Cardioprotective is a word you won't find in standard medical dictionaries.

But you will find it appearing in the medical literature. And you will be hearing it in medical discussions. Until dictionaries recognize the term, MSD invites you to use this as a working definition of *cardioprotective:*

"reduction of the risk of reinfarction and cardiac mortality for many stabilized post-MI patients."

We at MSD feel it is appropriate to bring you this definition of cardioprotective since it was MSD that brought you the impressive clinical data[1] that documented the cardioprotective benefits of BLOCADREN® (Timolol Maleate, MSD) for many stabilized patients who have survived the acute phase of a myocardial infarction.

[1]The Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction, N. Engl. J. Med. 304(14):801-807, April 2, 1981.

BLOCADREN is contraindicated in patients with bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see below); cardiogenic shock; and hypersensitivity to this product.

Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart

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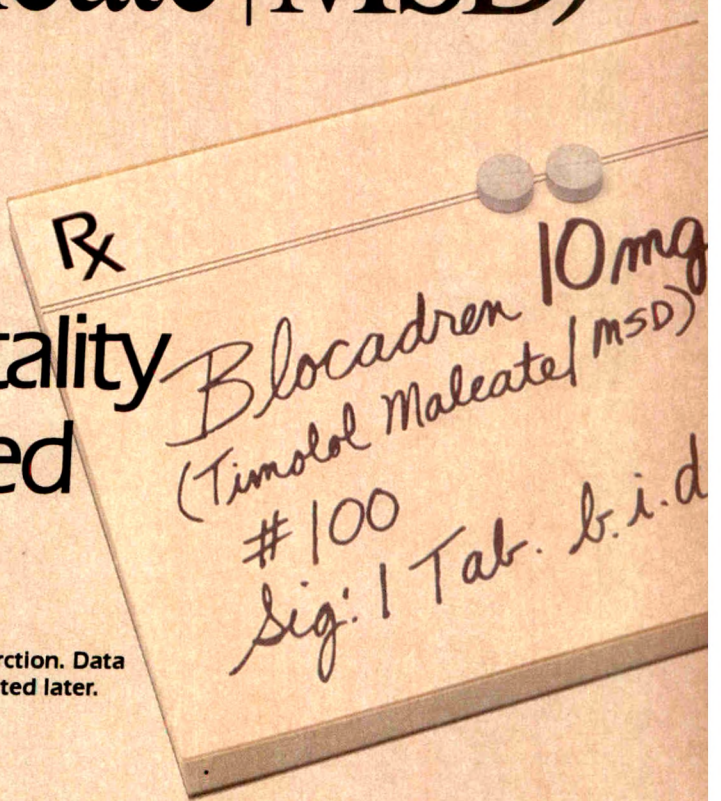
Blocadren®
(Timolol Maleate | MSD)

reduces the risk of reinfarction and cardiac mortality for many stabilized post-MI patients

Treatment should be initiated within 1 to 4 weeks after infarction. Data are not available as to whether benefit would ensue if initiated later.



disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

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For a Brief Summary of Prescribing Information, please see next page of this advertisement.

BLOCADREN®
(TIMOLOL MALEATE | MSD)

CONTRAINDICATIONS:

Bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to this product.

WARNINGS:

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In Patients without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS:

General: *Impaired Hepatic or Renal Function*: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Dosing in the Presence of Marked Renal Failure: Marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20-mg doses. Dosing in such patients should therefore be especially cautious.

Drug Interactions: Close observation of the patient is recommended when BLOCADREN is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

Pregnancy—Category C: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n = 176) %	Placebo (n = 168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
INTEGUMENTARY		
pruritus	1.1	0
NERVOUS SYSTEM		
dizziness	2.3	1.2
vertigo	0.6	0
paresthesia	0.6	0
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction*		Withdrawal†	
	Timolol (n = 945) %	Placebo (n = 939) %	Timolol (n = 945) %	Placebo (n = 93 %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure—Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema—Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

*When an adverse reaction recurred in a patient, it i listed only once.

†Only principal reason for withdrawal in each patient i listed.

These adverse reactions can also occur in patient treated for hypertension.

The following additional adverse effects have bee reported in clinical experience with the drug: *Body as Whole*: extremity pain, decreased exercise tolerance weight loss; *Cardiovascular*: cardiac failure, cerebra vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive*: gastrointestinal pain hepatomegaly, vomiting, diarrhea, dyspepsia; *Endocrine*: hyperglycemia, hypoglycemia; *Integumentary*: rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal*: arthralgia; *Nervous System*: local weakness *Psychiatric*: depression, nightmares, somnolence, insomnia, nervousness, diminished concentration; *Respiratory*: cough; *Special Senses*: visual disturbances, dry eyes *Urogenital*: impotence, urination difficulties.

Potential Adverse Effects: in addition, a variety of adverse effects not observed in clinical trials with BLOCADREN, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System*: reversible mental depression progressing to catatonia; hallucinations, acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular*: intensification of AV block (see CONTRAINDICATIONS) *Gastrointestinal*: mesenteric arterial thrombosis, ischemic colitis; *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Allergic*: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous*: reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

Clinical Laboratory Test Findings: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations.

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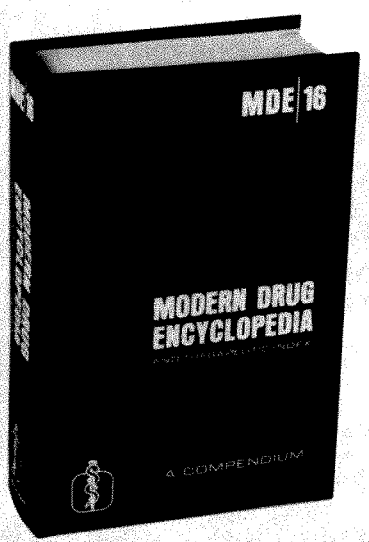
For more detailed information, consult your MSD Representative and the Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

--w th--r--" .. ".. i se is your drug reference?



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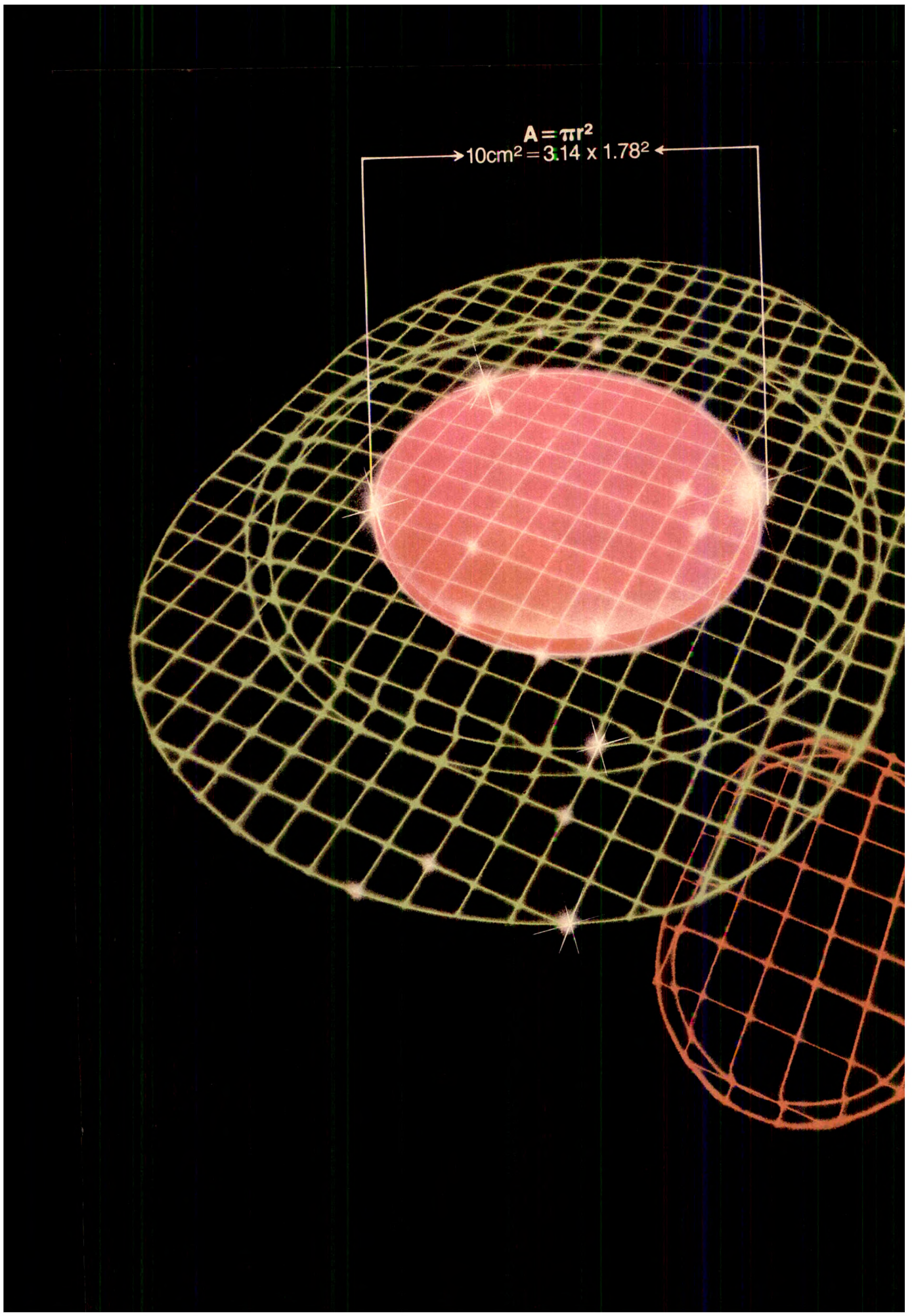

$A = \pi r^2$
$10cm^2 = 3.14 \times 1.78^2$

Designed with the patient in mind.

People move, bend, stretch, perspire.
When we designed Nitro-Dur™ (nitroglycerin) Transdermal Infusion System, we designed it with features to accommodate these human factors. Because of the size of Nitro-Dur it has features that other nitroglycerin systems don't have.

It's big because it's the only one with a wide adhesive strip.
If angina patients were supine for 24 hours, adhesion would be a minor concern. But people move, bend, stretch, and turn while awake and asleep. A system has to stay put throughout all these movements.

In developing Nitro-Dur, we tested dozens of tapes before we settled on a microporous tape known for its excellent adhesion, one that doesn't leave the skin macerated and is relatively painless on removal.

The Nitro-Dur adhesive strip is wider than that on any other system. Wide enough to stay put during a 24-hour day of walking, showering, bending, standing or sleeping. Wide enough to prevent leaking or falling off.

It's big because it's the only one with an absorbent pad.
Because perspiration could affect adhesion, we added an absorbent pad behind the matrix. Nitro-Dur is the only system with this feature.

Surface area determines the dose.
The stratum corneum regulates the absorption of cutaneously applied nitroglycerin. Therefore, as the surface area of application is increased the dose of nitroglycerin also increases. To insure a fixed surface area, we offer a solid—a gel polymer matrix that contains the active drug.

The only transdermal to offer you greater dosage flexibility.
Nitro-Dur has four dosage strengths—5, 10, 15 and 20 cm^2. Other systems limit your options to two strengths.

The only place it's smaller—the cost to your patients.
Your patients can save up to $75 a year using Nitro-Dur rather than competitive products. Considering that they may be taking the product for years, that's a very important advantage.[1]

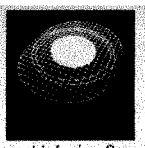
The human factor made us big. You made us the largest-selling transdermal nitroglycerin system.

The most widely prescribed transdermal nitroglycerin system.

Nitro-Dur™
(nitroglycerin)
Transdermal Infusion System

Please see next page for a summary of prescribing information.

Nitro-Dur™
(nitroglycerin)
Transdermal Infusion System



DESCRIPTION: The Nitro-Dur Transdermal Infusion System contains nitroglycerin in a gel-like matrix composed of glycerin, water (purified), lactose, polyvinyl alcohol, povidone and sodium citrate to provide a continuous source of the active ingredient. Nitro-Dur is available in dosage sizes 5cm², 10cm², 15cm² and 20cm², containing 26 mg, 51 mg, 77 mg and 104 mg of nitroglycerin, respectively, thereby providing precise dosing levels of nitroglycerin. Nitro-Dur has a rated release *in vivo* of approximately 0.5mg/cm²/24 hours. Each unit is sealed in a polyester-foil-polyethylene laminate. The bandage portion consists of a medical grade non-woven, heat sealable, microporous tape.

CLINICAL PHARMACOLOGY: When the Nitro-Dur system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In bioavailability studies[2] transdermal absorption of nitroglycerin from the gel-like matrix achieved steady state venous plasma levels comparable to that of sublingual nitroglycerin and maintained these levels for 24 hours. Therapeutic effect is achieved within 30 minutes after application of the unit, and persists about 30 minutes after removal of the unit.

INDICATIONS AND USAGE: Prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS: The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the Nitro-Dur dosage should be reduced or use of the product discontinued.

HOW SUPPLIED: Nitro-Dur Transdermal Infusion System, 5cm², 10cm², 15cm² and 20cm², is available in unit dose packages of 28.

CAUTION: Federal law prohibits dispensing without a prescription.

PATIENT INSTRUCTIONS FOR APPLICATION: Patient instructions are furnished with each unit dose package.

For complete prescribing information, please see package insert.

1082

References

1. Pharmacy acquisition cost (AWP), *Drug Topics Red Book*, 1982 (assuming a 50% markup).
2. Data on file: Key Pharmaceuticals, Inc.

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NOSOCOMIAL INFECTIONS

edited by
Richard E. Dixon, M.D.

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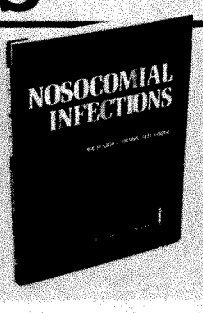

Based on the proceedings of the 2nd International Conference on Nosocomial Infections held August 5 - 8, 1980 in Atlanta, Georgia and sponsored by the Center for Disease Control, this book provides between two covers the most comprehensive, in-depth study of this international problem published in 10 years. This major reference is divided into 11 sections consisting of 50 chapters written by over 100 internationally known experts.

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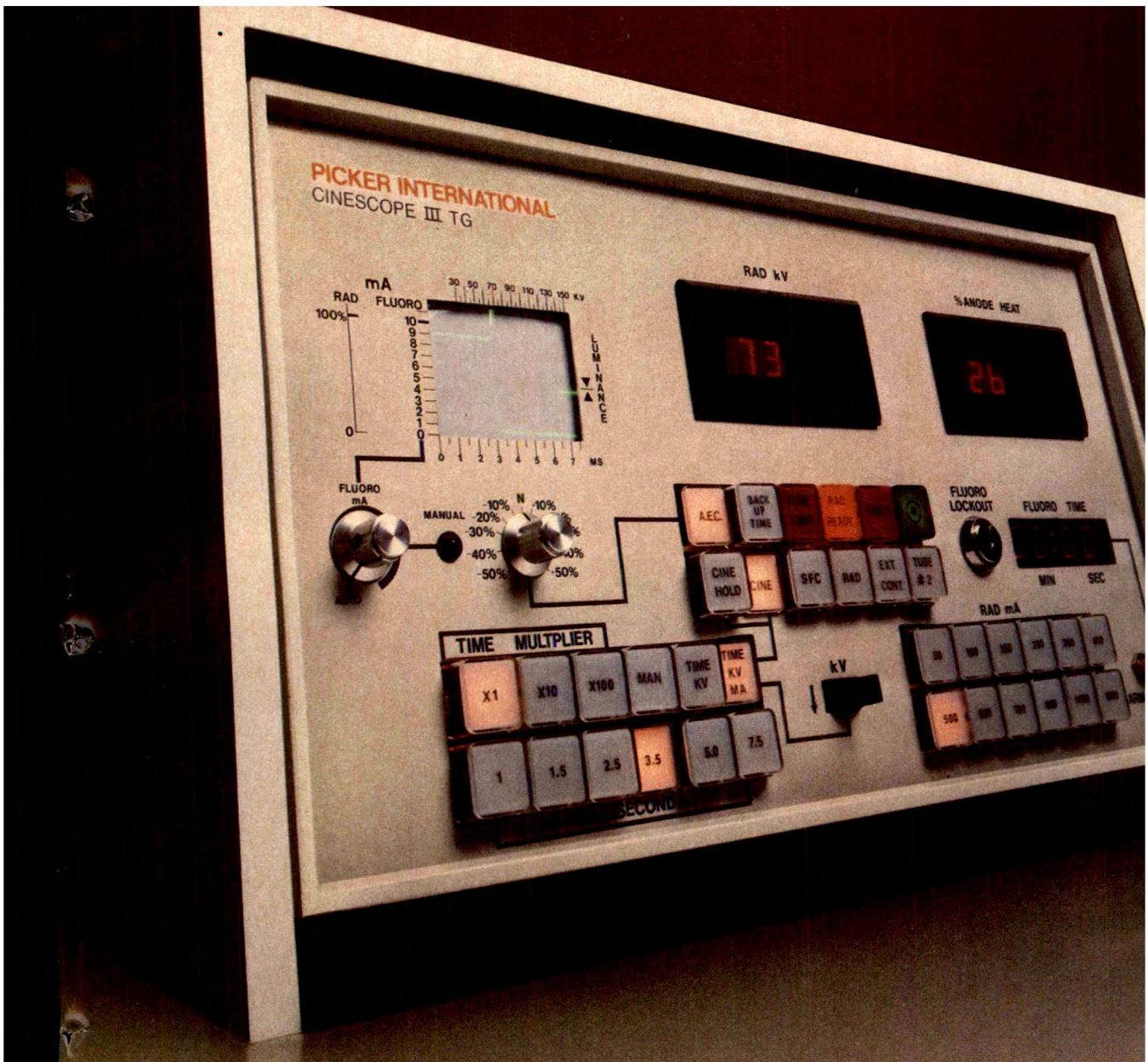

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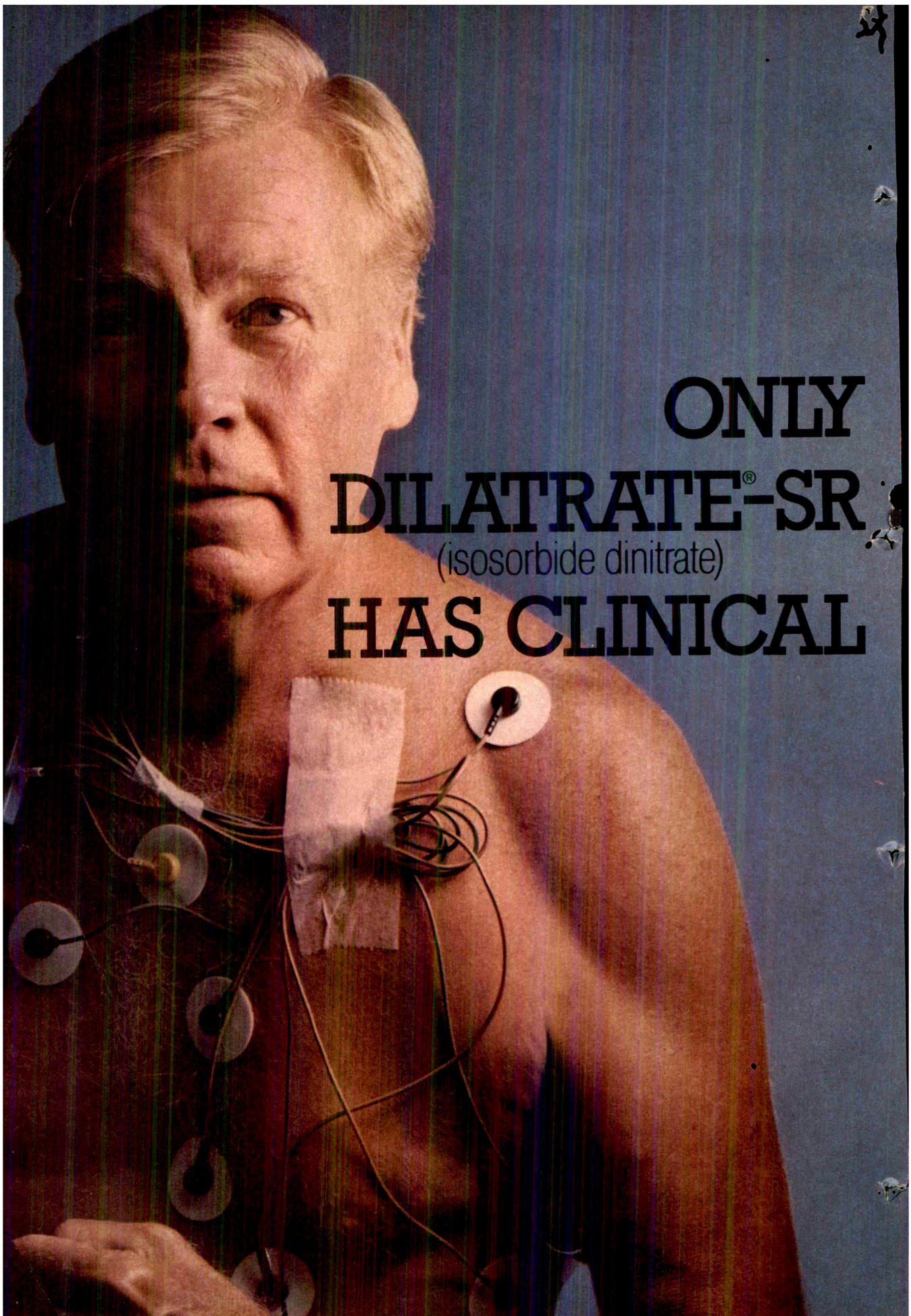
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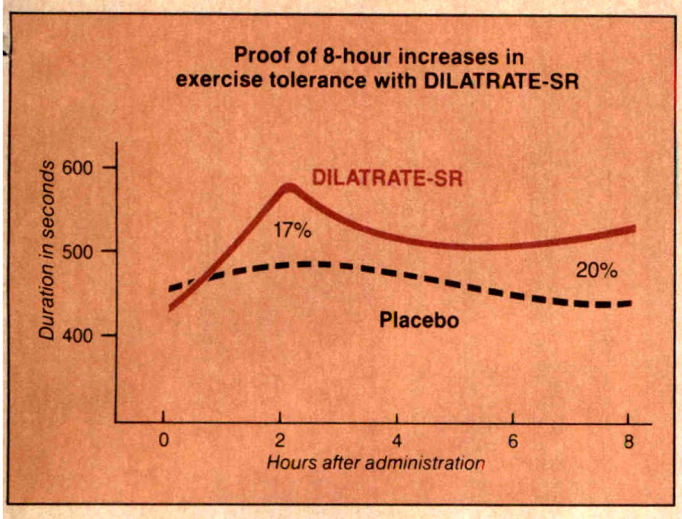

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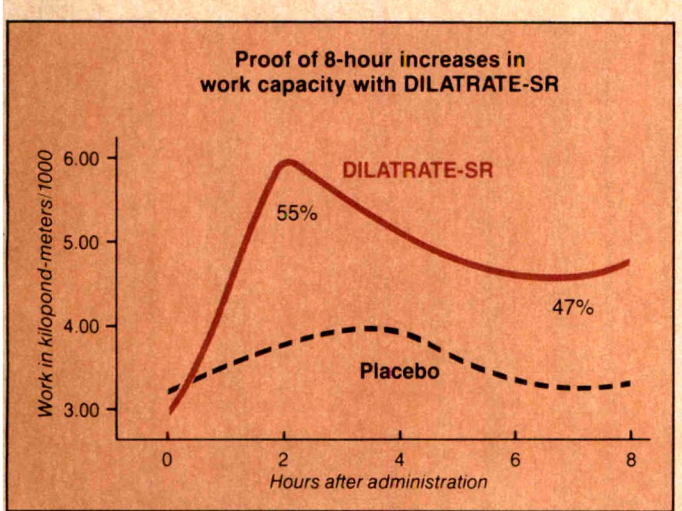

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1. DiBianco R et al: Effects of a new oral slow release form of isosorbide dinitrate on the hemodynamics and exercise capacity of patients with angina — a placebo controlled and double blind study. *Circulation* (Supp II) 66:381, Oct 1982.
2. Dinsdale J, Allen J: Data on file, Medical Department, Reed & Carnrick

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Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATION: Idiosyncrasy to this drug.

WARNINGS: Data supporting the use of nitrates and nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

PRECAUTIONS: Tolerance to this drug, and cross-tolerance to other nitrates or nitrites may occur.

In patients with functional or organic gastrointestinal hypermotility or malabsorption syndrome it is suggested that either the 5 mg. or 10 mg. oral tablets or 2.5 mg. or 5 mg. sublingual tablets be the preferred therapy.

ADVERSE REACTIONS: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

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written by:

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  Chief, Pathology Branch/National Heart, Lung & Blood Institute/National Institutes of Health/and Clinical Professor of Pathology & Medicine (Cardiology)/Georgetown University School of Medicine, Washington, D.C.
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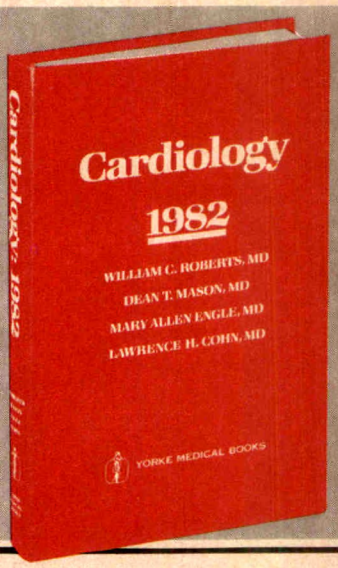

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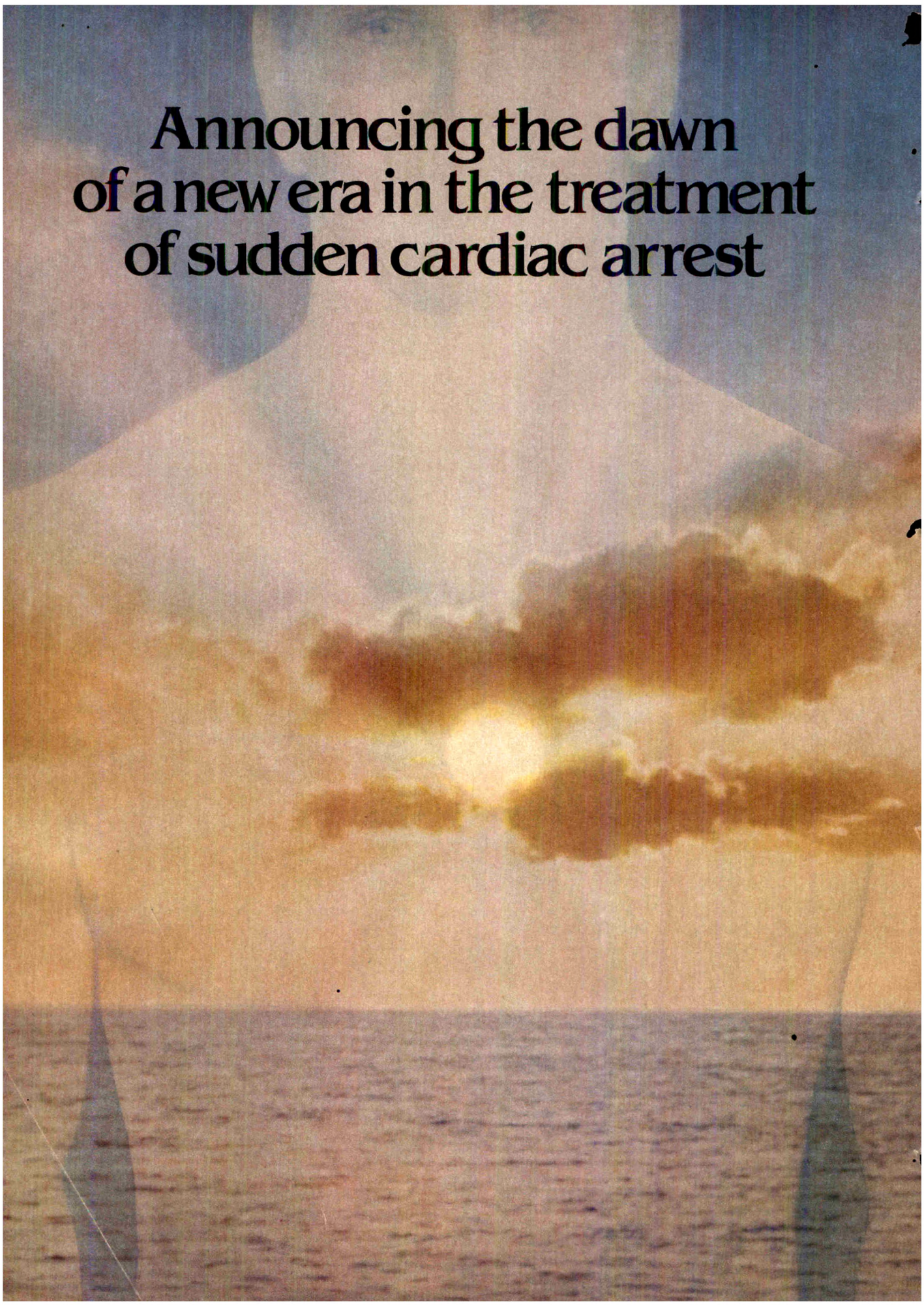
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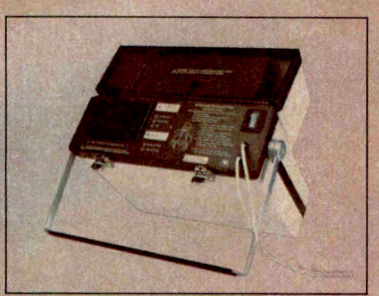

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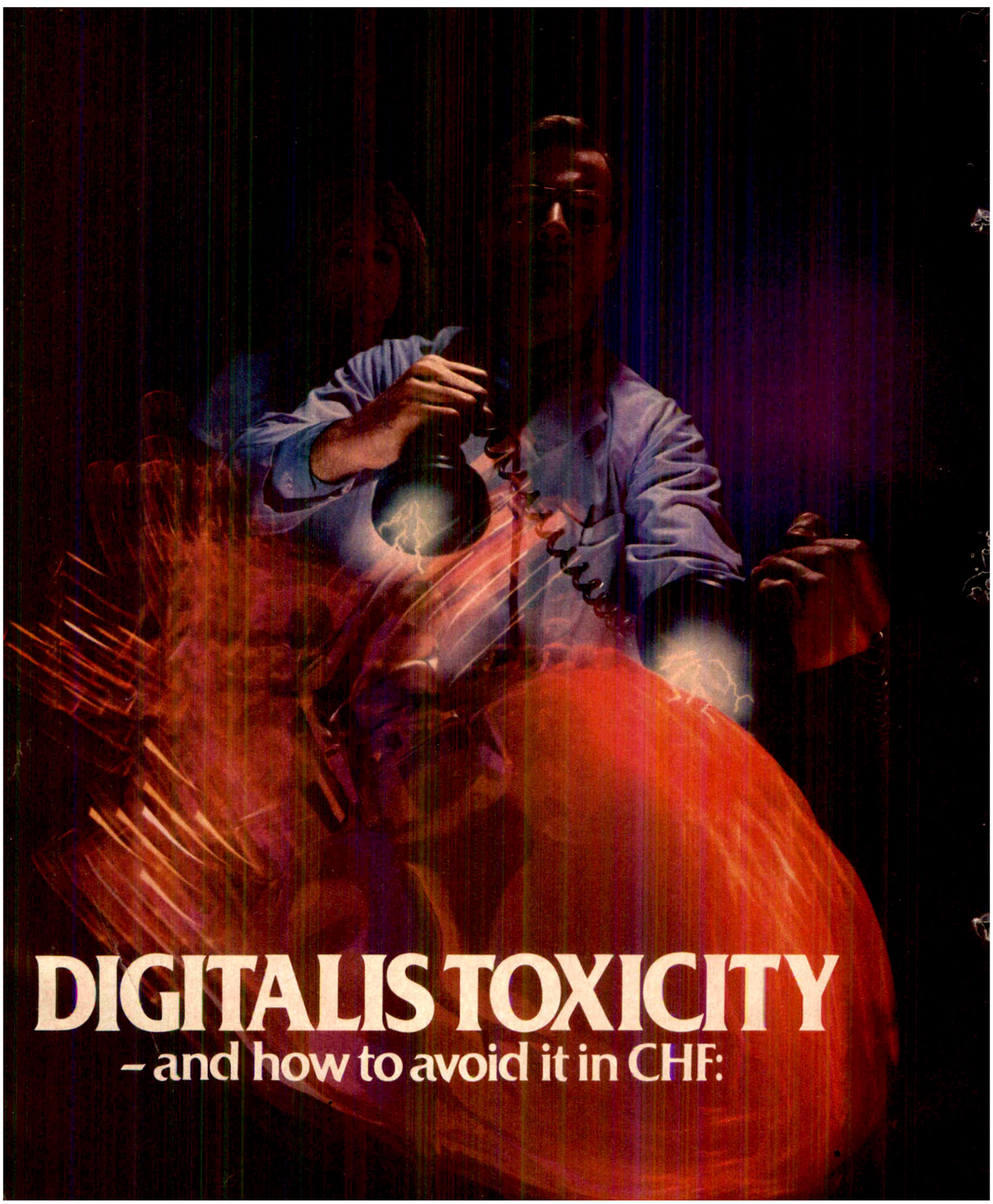
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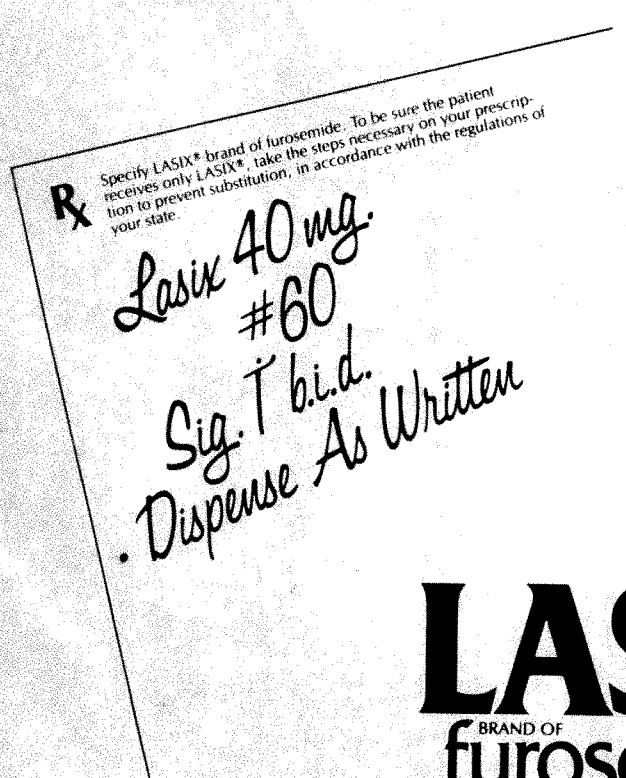

If you are in doubt about a particular generic furosemide, call the offices of the Food and Drug Administration's Bureau of Drugs, Consumer and Professional Relations staff at 301-443-1016.

Reference: 1. Koch H: Drugs most frequently used in office-based practice: National Ambulatory Medical Care Survey, 1980, Vital and Health Statistics of the Nat Ctr for Health Statistics, No. 78 (May 12) 1982.

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WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

PREGNANCY: Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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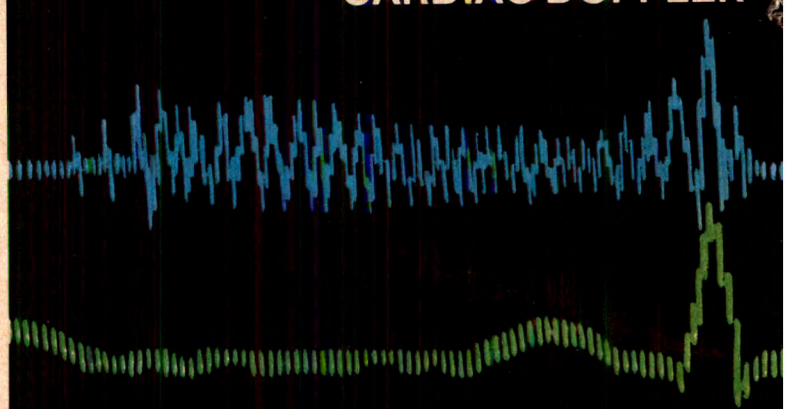

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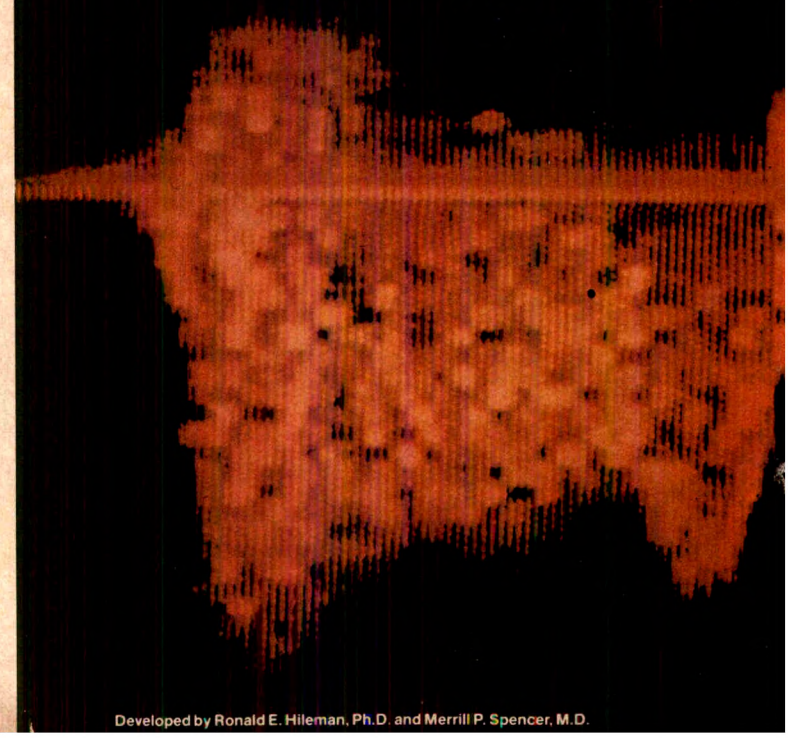

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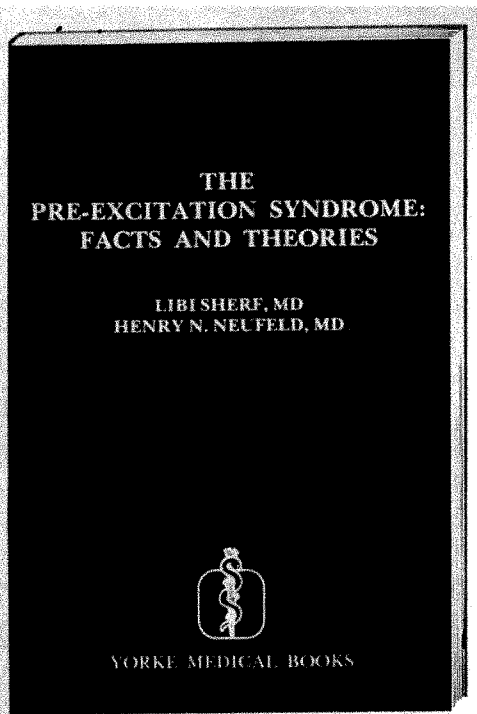

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SEPTEMBER 1978, 288 PAGES, 110 ILLUS, 1,000 REF.

Every Cardiologist, Internist, Pediatrician, Surgeon — Indeed, *Every Physician* — Should Have a Good Basic Knowledge of The Pre-excitation Syndrome. Here Are Just a Few Reasons Why This is so Essential:

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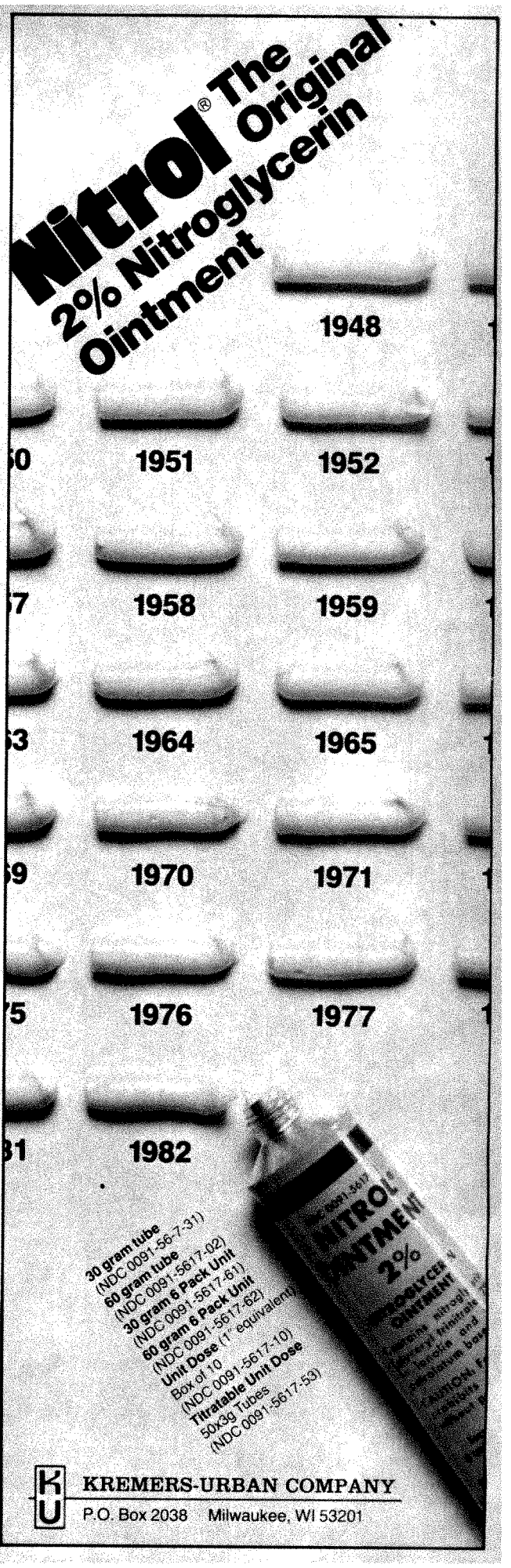

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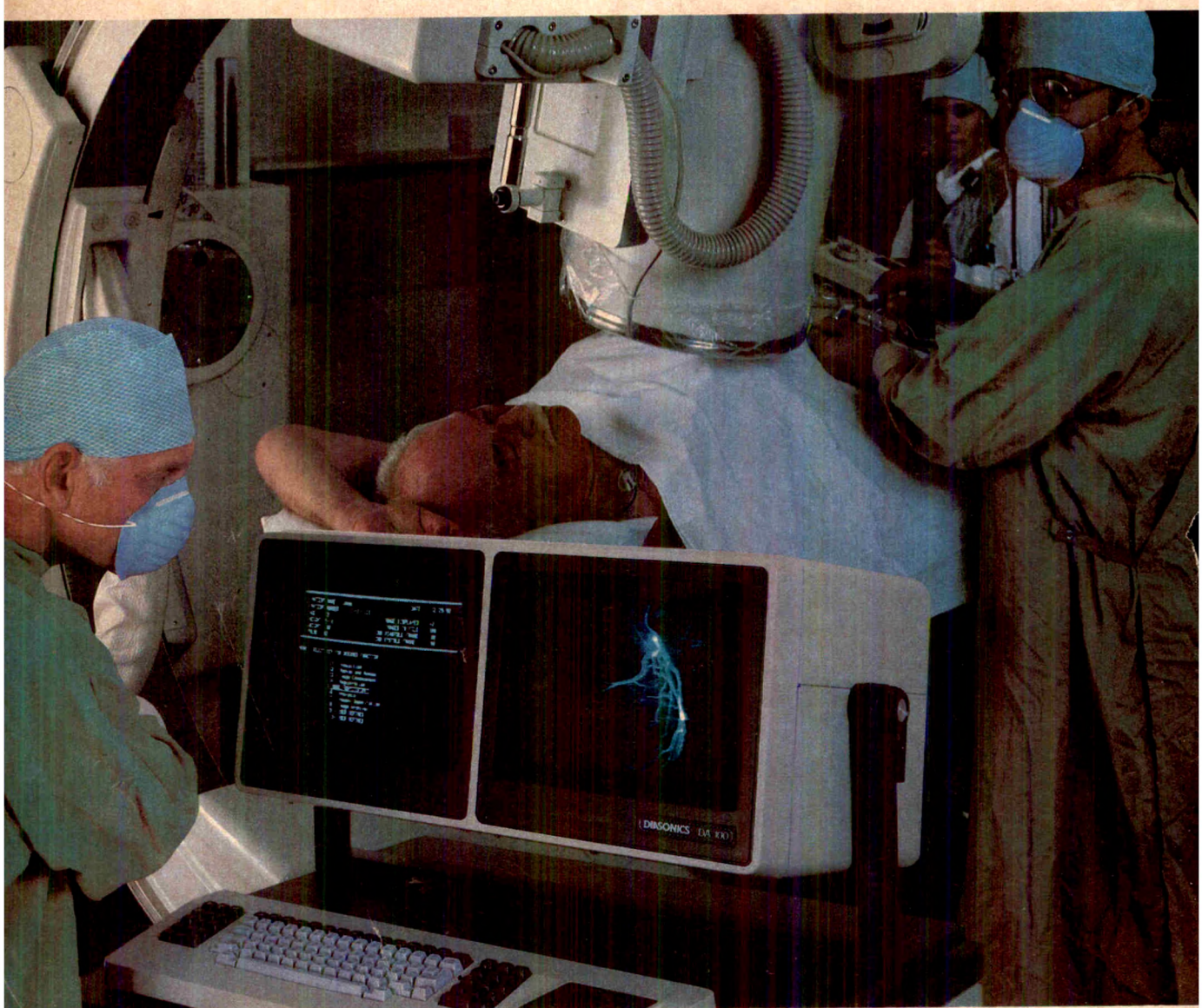

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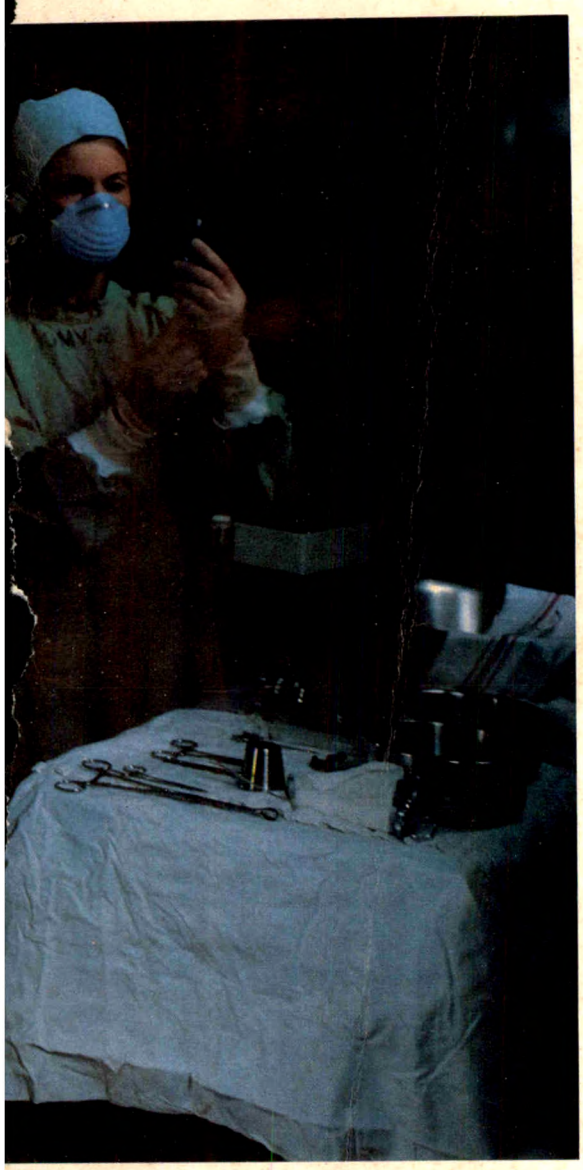

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